Chapter 162: Melanoma

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KEY CONCEPTS

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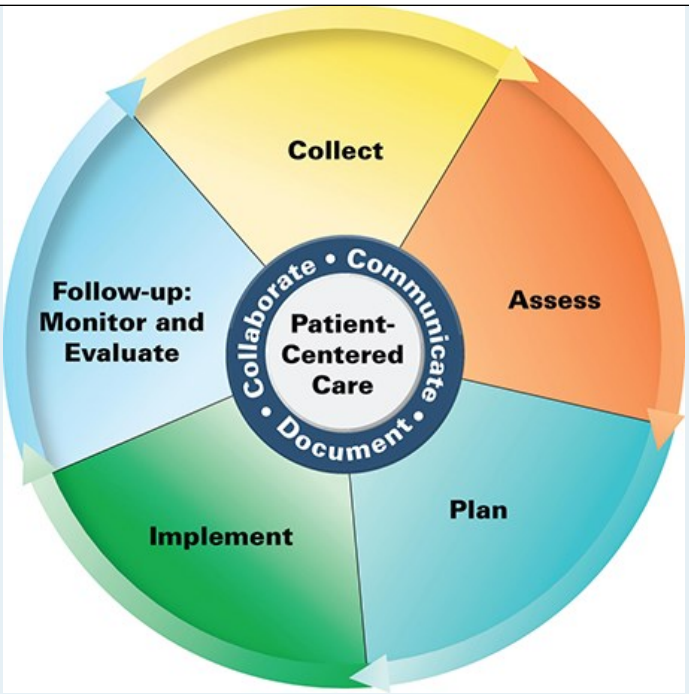
1. Cutaneous melanoma is an increasingly common malignancy that can be cured if detected early. Public education about screening and early detection is one strategy to reduce the mortality associated with cutaneous melanoma.
2. Surgical resection can cure patients with early-stage melanoma.
3. Adjuvant therapy should be considered in patients with locally advanced disease; recommended options include ipilimumab, nivolumab, pembrolizumab, BRAF and MEK inhibitors, and clinical trial.
4. Chemotherapy and biochemotherapy offer limited benefit in the treatment of metastatic melanoma.
5. Immunotherapy with ipilimumab, nivolumab, the combination of ipilimumab/nivolumab and pembrolizumab have led to durable responses and significantly prolonged overall survival in patients with metastatic melanoma.
6. Immune-related toxicities associated with immunotherapy can be severe and life-threatening. Consequently, the use of these agents warrants appropriate patient selection, close monitoring, and toxicity management by an experienced healthcare team.
7. As the biology of melanoma has been further delineated, a growing number of potential targets for drug therapy have been identified. *BRAF* mutations occur in up to 70% of melanoma patients. The combination of BRAF and MEK inhibitors improves overall survival in patients with this mutation.
8. Treatment of melanoma is determined by many factors. As the number of treatment options for patients with metastatic melanoma grows, disease- and patient-related factors should be considered to determine appropriate therapy.

PATIENT CARE PROCESS

Patient Care Process for Melanoma



Collect

- Patient characteristics (eg, age, sex, physical features)
- Patient medical history (personal/family) including autoimmune diseases
- Social history (eg, history of blistering sunburns; intermittent, intense sun exposure; tanning bed use)
- Current medications including OTC products, herbal products, dietary supplements, current or past use of immunosuppressants
- Objective data
  - Type of biopsy performed
  - Pathology report: Breslow thickness, presence or absence of ulceration, mitotic rate
  - Routine imaging and labs not recommended for early stage/localized disease; perform for baseline staging in stage IIIB or higher (can be considered for stage IIIA)
  - Labs: serum creatinine (SCr), liver function (AST, ALT, total bilirubin), lactate dehydrogenase (LDH), complete blood count (CBC), thyroid function (TSH, free T4) for regional/metastatic disease

Assess

- Appropriate primary treatment (wide excision, need for sentinel lymph node biopsy)
- Status of sentinel lymph node biopsy (if performed); if positive sentinel lymph node, appropriateness of nodal basin ultrasound surveillance versus complete lymph node dissection
- Mutational analysis, if appropriate
- Presence of active autoimmune disease
- Ability/willingness to complete 1 year of adjuvant treatment, if recommended

- Ability/willingness to pay for treatment options
- Ability/willingness to obtain laboratory monitoring tests and imaging to evaluate signs and symptoms
- Emotional status (eg, presence of anxiety, depression)

Plan

- Wide excision for all stages; consider sentinel lymph node biopsy for stage IB; offer to stage II
- Adjuvant treatment with either PD-1 inhibitor or BRAF and MEK inhibitor combination for patients with fully resected stage III or stage IV disease that are appropriate for therapy
- Drug therapy regimen including specific drug(s) dose, route, frequency, and duration (see Tables 162-7 and 162-8)
- Referral to neurosurgery for treatment of brain metastases (Gamma Knife stereotactic radiosurgery; resection by craniotomy)
- Monitoring parameters including efficacy (eg, CT and brain MRI as indicated) and safety (eg, signs and symptoms of immune-related adverse events [irAEs]); frequency and timing of follow-up
- Patient education (eg, purpose of treatment, drug-specific information, proper administration/storage/handling for targeted therapies, when to seek emergency medical attention; see Tables 162-7 to 162-10)
- Referrals to other specialists when appropriate (eg, endocrinology, GI)

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up

Follow-up: Monitor and Evaluate

- At least annual skin examination; self-examination of skin and lymph node
- Imaging to assess signs/symptoms and/or every 3 to 12 months to screen for recurrence
- Presence of adverse drug reactions
- Patient adherence to treatment plan using multiple sources of information

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Review educational materials regarding skin self-examinations created by the American Cancer Society (https://www.cancer.org/healthy/be-safe-in-sun/skin-exams.html) and the American Academy of Dermatology Association (https://www.aad.org/public/diseases/skin-cancer/find/check-skin). Assess the level of understanding and ease of use from a patient perspective for each. Then perform your own skin self-examination based on the ABCDE rule to identify any new or suspicious spots on your skin. This activity will enhance student understanding regarding the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Skin cancer is the most common malignancy worldwide and is associated with chronic ultraviolet (UV) exposure. The two types of skin cancer are nonmelanoma skin cancers (NMSCs) and melanoma. Although NMSCs are the most common malignancy of the skin, cutaneous melanoma accounts for up to 80% of all skin cancer-related deaths.[1] Melanoma cases are increasing globally with the highest rates found in Australia, New Zealand, North America, and Northern Europe.[2] Melanoma is the fifth most common cancer in the United States.[1] The incidence of melanoma has rapidly increased in the United States over the last 30 years, and has increased an average of 1.4% each year over the last decade.[3] When detected early, patients generally have a good prognosis. Skin cancer prevention and screening have a major impact on public health and the success of treatment for those individuals diagnosed with NMSC and melanoma. Skin cancers tend to occur more frequently in older individuals with a median age of diagnosis of 65 years.[3] Therefore, as the population continues to age, effective strategies to prevent, detect, and treat individuals with these cancers are necessary. An understanding of the biology of melanoma has led to the development of therapies targeted toward somatic mutations and the immune response, which have shown improved outcomes in patients with advanced melanoma.

EPIDEMIOLOGY

In the United States, it is estimated that 99,780 cases of melanoma will be diagnosed in 2022, accounting for 7,650 deaths.[4] The overall incidence is greater in men than women, but rates are higher in women before the age of 50. Risk also varies with ethnicity, with most melanoma cases occurring among White individuals.[4] Childhood and adolescent melanoma account for only 1% and 3%, respectively, of new melanoma cases each year but is the most common skin cancer in individuals younger than 20 years.[5] The majority of childhood and adolescent melanoma occurs in females and non-Hispanic White patients.[6] From the 1970s to the early 2000s, the incidence of melanoma in those younger than 20 years increased by 2% to 3% per year, but data from 2004 to 2010 show a decrease of 11.6% per year.[6]

Survival rates for patients with melanoma have gradually increased over the past four decades. Due to recent advances in treatment, the 5-year relative survival rate is 93.3% for all stages of melanoma, but survival declines to 29.8% in patients with more advanced disease.[3] Over the last decade, the death rate from melanoma has declined around 1% per year in adults older than 50 years and 3% per year in adults younger than 50 years.[3]

Several patient-specific and environmental risk factors have been identified (see Table 162-1), and it is likely these factors alone, or in combination, increase the risk of cutaneous melanoma.

TABLE 162-1

Risk Factors for Melanoma

Patient-Specific Risk Factors
Adulthood (older than 15 years)
History of cutaneous melanoma
Dysplastic nevi
High density of common nevi and atypical nevi
Cutaneous melanoma in first-degree relative
Immunodeficiency or immunosuppression
High degree of freckling
Sunburns easily or tans rarely
Blonde or red hair
Blue, green, or gray eyes
Socioeconomic status (higher > lower)
Race (Caucasians > Hispanics > African Americans)
External Risk Factors
Intense, intermittent sun exposures
History of sunburn
More than four painful sunburns before the age of 15 years
Recreational sun exposure

Both UVB and UVA are known carcinogens and are related to the development of melanoma. Caucasian individuals with fair-colored hair (red or blond), light-colored eyes (blue or green), high degrees of freckling, and those who tend to burn and rarely tan with sun exposure, are especially at risk. Clinical and epidemiologic research shows a higher rate of melanoma in those who have extensive or repeated intense UV and sun exposure.[1] Intermittent, intense sun exposure, blistering sunburns, tanning bed use, and the time of life when exposed to the sun are critical factors for the development of cutaneous melanoma.[7,8] The risk of melanoma seems to be greater during childhood and adolescence due to sunlight and UV radiation exposure and lower in adults who have had chronic sun exposure, are without a history of burning, and those with occupational exposure.

A significant risk factor for melanoma is the number and size of melanocytic nevi (pigmented lesions or moles) on the body. The formation of these nevi is directly related to cumulative sun exposure. The relative risk of developing melanoma increases with the number of typical nevi on an individual. A second risk factor is the presence of atypical melanocytic nevi. Atypical nevi may progress from a normal nevus or be dysplastic from the onset. Up to 20% of melanomas develop from atypical nevi. Congenital melanocytic nevi may be present at birth or within the first few months of life, and the associated risk of melanoma increases with size.[1,6]

Other risk factors in the development of melanoma include immunodeficiency (either inherited or acquired), a personal history of NMSC or melanoma skin cancer, and a diagnosis of xeroderma pigmentosum, a rare skin disorder. Patients with these risk factors often have more aggressive disease and have been shown to have a poor prognosis.[1,6]

Family history is associated with up to 10% of cases of melanoma. Familial atypical multiple mole syndrome (FAMMM) or dysplastic nevus syndrome is an autosomal dominant hereditary disease that accounts for about 1% of melanoma cases. It is characterized by the presence of numerous common and atypical moles and a family history of melanoma in multiple first-degree relatives and younger age at diagnosis.[9,10] Patients with FAMMM syndrome are at considerable risk for developing melanoma which increases with age. FAMMM syndrome is associated with mutations in the *CDKN2A* gene. *CDKN2A* encodes two distinct proteins: p16, an inhibitor of cyclin-dependent kinase 4 and 6, and p14ARF, which inhibits p53 degradation.

Mutations in *CDKN2A* result in increased proliferation and decreased apoptosis.[9,10]

ETIOLOGY

Melanoma arises from the melanocytes in the basal layer of the epidermis. DNA damage, most commonly a result of UV radiation, leads to cellular mutations that transform the cell and result in uncontrolled proliferation and the formation of tumors. The identification of these genetic alterations has led to the recognition of molecular subgroups of melanoma and more focused drug development for treatment.

A major signaling pathway associated with the development of melanoma is the mitogen-activated protein kinase pathway (MAPK), which mediates receptor tyrosine kinases, resulting in activation of RAS and downstream BRAF. Activating *BRAF* mutations are the most common somatic genetic event in human melanoma, occurring in about 50% of melanoma patients and primarily noted by a single point mutation at residue V600. The V600E mutation, in which valine is substituted for glutamic acid at codon 600, is the most common point mutation. The V600K mutation may also occur at this residue. *BRAF* mutations are associated with younger age at diagnosis, intermittent sun exposure, and superficial spreading melanoma.[10]

Upstream of BRAF, mutations in *NRAS,* and *KIT* can act as molecular drivers in the development of melanoma. Mutations in *NRAS* are found in up to 20% of patients. These tumors are associated with chronic sun exposure and high growth rates.[7] *KIT* is a transmembrane receptor tyrosine kinase that, when activated, signals the MAPK and phosphatidyl-inositol-3-OH kinase (PI3K) pathways, resulting in transcription and cell proliferation. Mutations in *KIT* are commonly found in acral and mucosal melanomas as well as those with chronic sun exposure.[10]

Other genetic alterations involved in the development of melanoma include *MITF* (microphthalmia-associated transcription factor) and *MCIR* (melanocortin 1 receptor gene). *MITF* is a gene important to the survival of melanocytes and, when mutated, acts as an oncogene. *MCIR* is prevalent in individuals with melanoma and signals through the MITF pathway. It is involved in melanin synthesis and is associated with the red hair and fair skin phenotype.[10]

PATHOPHYSIOLOGY

Melanomas most often arise within epidermal melanocytes of the skin, although they can also arise from noncutaneous melanocytes. During fetal development, melanocytes migrate over a predictable route to multiple sites within the body, including the skin, uveal tract, meninges, and ectodermal mucosa. Melanocytes synthesize melanin to protect various tissues, such as the skin, from UV damage and reach the keratinocytes in the upper layers of the epidermis via dendrites. Primary melanoma can arise in any area of the body with melanocytes. Cutaneous melanoma is the most frequent site constituting 90% of all melanomas. Other sites of primary melanoma include the eye (uveal melanoma), the mucosa, and in some cases, as metastatic disease with an unknown primary site.[10]

The pathogenesis of human melanoma involves a series of morphologic stages: melanocytic atypia, atypical melanocytic hyperplasia, radial growth phase, vertical growth phase with or without in-transit metastasis, regional lymph node metastatic melanoma, and distant metastatic melanoma. Melanoma gains the potential for metastasis with the onset of a vertical growth phase. Therefore, the thickness of a primary melanoma is an important prognostic factor and is used in the staging classification of cutaneous melanoma. As the disease progresses, melanoma cells increase the production of certain growth factors and cytokines which, in turn, activate cellular growth and survival pathways, including the MAPK, PI3K/AKT, and mammalian target of rapamycin (mTOR). Understanding the biology of melanoma has provided targets for innovative drug therapy.

The role of the immune system in the development of melanoma is well documented and spontaneous cancer regressions associated with host immunity have been reported.[11] Melanoma cells evade the immune system by exploiting immune checkpoints. Immune checkpoint receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death-1 (PD-1) are found on the surface of activated T cells and, when bound to a ligand, inhibit the function of the T cell. In the case of PD-1, when interferon is released by T-cell recognition of the melanoma cell, janus-kinase (JAK) and signal-transducer-and-activator-of-transcription (STAT) are upregulated, leading to increased expression of programmed cell death ligand 1 (PD-L1) on the melanoma cell surface. When PD-L1 binds to PD-1, the T cell becomes inactivated and the antitumor immune response is inhibited.[7]

MELANOMA SUBTYPES

Histologic

Cutaneous melanomas are categorized by growth patterns. Four major histologic subtypes, or growth patterns of primary cutaneous melanoma, have been identified: superficial spreading melanoma (SSM), nodular melanoma (NM), lentigo maligna melanoma (LMM), and acral lentiginous melanoma (ALM). While these subtypes do not directly correlate with clinical outcomes, certain subtypes have been shown to demonstrate a higher frequency of genetic mutations.

SSM is the most common type of cutaneous melanoma, accounting for up to 70% of all melanomas and is associated with intense, intermittent sun exposure. Early in lesion development, SSM is flat, growing radially before vertically. SSM evolves slowly, typically over 1 to 5 years. As the lesion progresses, it may become raised or ulcerated. The borders are often irregular and asymmetrical as the lesion progresses and may vary in color (blue, black, brown, pink, or other colors). SSMs may occur at any anatomic site on the body but are more commonly found on the trunk and extremities. The average age of a diagnosis of SSM is 50 years. These lesions can be linked to mutations in *BRAF*.

Nodular melanoma is the second most common histological type of melanoma, occurring in 15% to 30% of patients. Since nodular melanoma is a pure vertical growth phase disease, it is more aggressive and develops more rapidly than other subtypes.[10] Nodular melanomas are often dark blue–black and uniform in color with a shiny surface, although a small percentage of nodular melanomas are amelanotic and have a fleshy appearance. Nodular melanomas are raised, often symmetric, and can occur at any site. *LMM* represents 10% to 20% of melanomas and is commonly found on the head and neck. It is unique from other histologic subtypes; it does not have the same propensity to metastasize because of a prolonged radial growth phase. LMM arises on chronically sun-exposed sites in older individuals and presents as a freckle-like lesion. LMMs are generally large flat, tan-colored lesions with shades of brown and black that gradually grow, develop, and begin to change in color.[10] Evolution into invasive melanoma is characterized by nodular development within the flat lesion. These lesions can be linked to mutations in *KIT*.

ALM makes up about 5% of melanomas and is not related to UV exposure. It presents commonly as melanoma on the palms of the hands or soles of the feet but may present as subungual melanoma and mucosal melanoma. ALMs located on the soles of the feet appear as a large tan or brown stain. The lesions often have irregular convoluted borders and may be masked by thick skin on the feet. Subungual melanoma arises in the nail matrix or nail bed. The most common presentation is a brown or black line in the great toe or the thumbnail. Mucosal melanoma is rare and can occur on any mucosal surface. Most commonly is seen in the oropharyngeal mucosa followed by the anal and rectal, genital, and urinary mucosa. Unfortunately, mucosal melanoma often does not become clinically apparent until the mass is large or the lesion bleeds. ALM is the most common type of melanoma reported in individuals with a dark complexion.[10] Similar to LMMs, this subtype is characterized by a protracted radial growth phase and is associated with mutations in *KIT*.

Uveal melanoma arises from the pigmented epithelium of the choroid. It is the most common primary intraocular malignancy seen in adults but is an uncommon tumor. Unlike cutaneous melanoma, the frequency and mortality rates of uveal melanoma have remained steady.[12] The risk of metastasis varies with the histologic type and size of the tumor and the location in the eye. The liver is the most frequent site of metastasis but uveal melanoma can spread to a variety of tissues.[10]

Clinical

Based on our understanding of the role of genetic alterations in the treatment and outcomes of patients with melanoma, four distinctive clinical subtypes have emerged based on UV exposure and anatomic site. The four subtypes are divided into (1) nonchronic sun damage (non-CSD): melanomas on the skin without chronic sun-induced damage; (2) chronic sun damage (CSD): melanomas on the skin with chronic sun-induced damage characterized by the presence of solar elastosis; (3) acral; and (4) mucosal.[8] The primary genetic differences of these subtypes are based on the activation of the MAPK and PI3K pathways. *BRAF* mutations predominantly occur in non-CSD (56%) and less commonly in the other groups. About 5% to 20% of all the subtypes contain *NRAS* mutations and these mutations occur independent of *BRAF*. Further studies showed *KIT* mutations are found in almost 40% of acral and mucosal subtypes, in almost one-third of CSD melanomas and not at all in non-CSD melanomas.[8] Guidelines recommend uveal and mucosal melanoma be treated differently than CSD and non-CSD melanoma because of their differences in presentation and outcomes.[8] This further emphasizes the need for continued refinement of tumor classifications in melanoma based on genetic and biological features, which will lead to more personalized treatment options and improved outcomes for patients.

PREVENTION AND DETECTION

Skin cancer is a major health problem in the United States. In 2014, the US Surgeon General released a Call to Action to Prevent Skin Cancer that addressed the following goals to support skin cancer prevention: increase opportunities for sun protection in outdoor settings; provide individuals with the information they need to make informed, healthy choices about UV radiation exposure; promote policies to advance the national goal of preventing skin cancer; reduce harms from indoor tanning; and strengthen research, surveillance, monitoring, and evaluation related to skin cancer prevention.[13]

Both UVA and UVB exposure plays a major role in melanoma development and is the most preventable cause of melanoma. The incidence of melanoma has been associated with latitude and the intensity of solar exposure among susceptible populations. As such, the mainstay of melanoma prevention remains strategies to protect individuals from the harmful effects of the sun (see Table 162-2).

TABLE 162-2

Options for Sun Protection

	Sunscreens	
Behavioral	**Physical Blockers (Reflectants)**	**Chemical Absorbers**
Protective clothing and accessories Seek shade (avoid peak sun hours) Avoid tanning equipment	Zinc oxide Talc Titanium dioxide Red petrolatum	Ultraviolet B absorbers Salicylates Cinnamates Camphor derivatives Aminobenzoates Ultraviolet A absorbers Benzophenone-6 Dibenzoylmethanes

Strategies such as sun avoidance, especially during peak hours of sun intensity (10 AM–4 PM), seeking the shade when outdoors, and use of protective clothing are important education concepts for individuals who are in the sun for prolonged periods or who are at high risk for burning. In addition, the use of sunglasses, with both UVA and UVB protection, is important. Due to its correlation with the development of melanoma, the World Health Organization International Agency for Research on Cancer has declared UV light emitted from tanning beds a human carcinogen and the United States Food and Drug Administration (FDA) reclassified UV tanning devices to class II (moderate-to-high risk) devices.[14] As a result, 44 states have regulations in place to restrict minors' access to indoor tanning, including 23 that prohibit the use of indoor tanning for anyone younger than 18 years.

Sunscreens are another strategy to decrease UV exposure. A broad-spectrum sunscreen with both UVA and UVB protection and an SPF of 15 or higher used regularly as directed is recommended with other sun protective measures to prevent sunburn and reduce the risk of skin cancer. Of note, current regulations limit the SPF value on sunscreen labels to 50+ because of the lack of evidence to show that products with SPF values greater than 50 provide greater protection.[15] However, the FDA proposed several changes regarding labeling requirements and reducing the number of active ingredients to be generally recognized as safe and effective for over-the-counter sunscreen products. It is important to counsel patients about the appropriate use of sunscreen. Sunscreen should be applied 30 minutes before going into the sun and reapplied every 2 hours, after swimming or after perspiring heavily. About one ounce (30 mL) of sunscreen (a "palmful") should be used to cover the arms, legs, neck, and face of the average adult. Sun protection must be used regularly and not merely limited to times of recreation or anticipated "prolonged" exposure.

There are no consistent recommendations for the screening and early detection of melanoma. Early detection can play a large part in preventing a premalignant precursor from becoming melanoma or preventing a melanoma recurrence. About 50% of initial melanoma lesions are discovered by self-skin examination (SSE). Improved survival rates for melanoma have been attributed to the identification and treatment of disease at an early stage when the disease is limited and has not yet metastasized. High-risk patients with a strong family history should have additional clinical examinations, and in some cases, screening photography to document the size, shape, and location of moles. The entire cutaneous surface, including the scalp, should be examined. Both patients and clinicians need to be properly educated in the clinical features of the disease to ensure a more appropriate

diagnosis.

In some cases, an individual may need the help of a partner or caregiver to perform an SSE. This is especially important for older adults as they are more likely to develop and die from melanoma. Barriers to successful SSEs in older adults, such as failing eyesight, lack of partners, and poor memory impact older adults in detecting new or changing lesions. These barriers, coupled with the higher incidence of melanoma in older adults, present challenges and opportunities for healthcare professionals to target education on this growing segment of our population.

Healthcare professionals who routinely work with the public have an opportunity to increase public awareness concerning the benefits and appropriate methods for SSE. Educational pamphlets describing SSE (see Table 162-3) for the public are widely available through the American Cancer Society, American Academy of Dermatology, and Skin Cancer Foundation. If a newly discovered pigmented lesion is identified on SSE, or if a preexisting pigmented lesion changes, the individual should be immediately evaluated by a clinician.

TABLE 162-3

Self-Examination of Suspicious Moles

1. Examine your body front and back in the mirror and then the right and left sides with the arms raised
2. Bend the elbows and look carefully at the forearms and upper arms and palms
3. Look at the backs of the legs and feet. Look specifically in the spaces between toes and at the soles of the feet
4. Examine the back of the neck and scalp with the help of a hand-held mirror; part the hair (or use a blow dryer) to lift the hair and give yourself a closer look
5. Check the back and buttocks with a handheld mirror

Data from the American Academy of Dermatology (www.aad.org).

Benign nevi often occur in sun-exposed areas and are typically 4 to 6 mm in diameter (about the size of a pencil eraser), raised or flat, uniform in color and round in shape. Dysplastic nevi, an intermediate between benign nevi and melanoma, tend to be larger than common nevi (>5 mm), appear as flat macules with asymmetry, have a fuzzy or ill-defined shape, and vary in color.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Melanoma

General

- Any lesion that changes in appearance over time

Local Signs and Symptoms

- The clinical features used to describe suspicious lesions are highlighted with the mnemonic "ABCDE"
  - Asymmetry: Melanoma lesions are often asymmetric
  - Border: Melanoma lesions have irregular borders
  - Color: Color is often variegated in a melanoma ranging from tan, blue-black, red, purple, or white
  - Diameter: Melanoma lesions are frequently greater than 6 mm
  - Enlargement or evolution: A sudden enlargement or change in the lesion is concerning for melanoma
- Other signs of melanoma include a lesion that swells, bleeds, or oozes

Systemic Signs and Symptoms

- Palpable lymph nodes
- Depending on the site of metastasis, shortness of breath, abdominal pain, bone pain, headache, and mental status changes

Laboratory Tests

- In addition to a comprehensive metabolic panel, LDH should be evaluated

Other Diagnostic Tests

- Biopsy and pathology review for staging with molecular testing for *BRAF, NRAS,* and *KIT*
- When applicable, SLNB
- Systemic staging should include chest, abdomen, and pelvic CT scan or CT/PET bone scan, and brain MRI

CT, computed tomography; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET, positron emission tomography; SLNB, sentinel lymph node biopsy.

The initial clinical presentation of melanoma is often a cutaneous pigmented skin lesion that changes over time. Any changes in the skin surrounding a nevus, including redness or swelling, are important clinical signs. Uncommonly, the lesion may become itchy or tender and painful. Friability of the lesion, resulting in bleeding or oozing, is a danger sign. Perhaps the most important warning sign of danger is the evolution of any characteristic of a lesion. A biopsy of the lesion is critical to establish the diagnosis of melanoma. Subsequent pathologic interpretation of the biopsy will provide information on prognosis and treatment options. An excisional biopsy, with a 1- to 3-mm margin of normal appearing skin, is recommended for a suspicious lesion and should include a portion of underlying subcutaneous fat for microstaging. For larger lesions, an incisional or punch biopsy can be performed and should include a core of full-thickness skin and subcutaneous tissue. When excisional biopsies are not appropriate, as with the face or palmar surface of the hands, a full-thickness incisional or punch biopsy is preferred. A shave biopsy is rarely appropriate because it can underestimate the thickness of the lesion, and may not fully remove it. A broad shave biopsy could be considered for melanoma in site or LMM. Evaluation of any individual with a suspected melanoma includes a complete history and total-body skin examination. The focus of the patient history is to identify potential risk factors including family history of melanoma, personal history of skin cancer or nevus excisions, immunosuppression or an immunosuppressive condition, sun exposure, tanning bed use, and phenotype. A total dermatologic examination is necessary to determine melanoma risk factors (eg, mole pattern, mole type, or freckling) and for staging. Since melanoma commonly spreads to the lymph nodes, individuals suspicious

for advanced disease should be examined for lymphadenopathy. Lactate dehydrogenase (LDH) should be measured because elevated serum levels are an independent predictor of decreased survival.[8,16] In addition, any other signs or symptoms suggestive of metastatic disease should be completely evaluated.

STAGING AND PROGNOSTIC FACTORS

The size of a primary melanoma lesion is associated with the likelihood of metastasis. The Breslow tumor thickness of the lesion is commonly used as a prognostic factor to predict outcomes.[6] Tumor thickness is quantified to the nearest 0.1 mm with an ocular micrometer, measuring from the top of the granular layer of the overlying epidermis to the deepest contiguous invasive melanoma cell. The correlation between tumor thickness and the risk of tumor metastasis is strong but does not include aspects such as tumor satellites, defined rather arbitrarily, as skin involvement within 2 cm of the primary lesion, and vascular invasion. Patients with satellitosis have a worse prognosis than patients with thick primary lesions (tumor thickness > 4 mm), and the prognosis is more similar to that of patients with nodal metastasis. The American Joint Committee on Cancer (AJCC) developed an early-staging system for melanoma that divides patients with localized melanoma into four stages according to the microstaging criteria of Breslow. Additionally, ulceration of the melanoma, satellite lesions of the primary tumor, and location of distant metastases must be considered for accurate staging. As a result, the revised AJCC staging system for cutaneous melanoma was implemented in 2018.[16] Carefully examine older clinical trials to determine which staging system was used to determine patient inclusion and exclusion criteria, as results may differ based on these patient criteria. Clinical staging includes microstaging the primary melanoma with clinical, laboratory, and radiologic evaluation. It is used after complete excision of the primary melanoma and clinical assessment to determine regional and distant metastasis. Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional nodes after partial or complete lymphadenectomy. Patients with limited disease (in situ, stage 0 or stage 1A) do not require pathologic evaluation of lymph nodes (see Tables 162-4 and 162-5).[8]

TABLE 162-4

Melanoma Tumor (T), Node (N), Metastasis (M) Classification

T Classification	Thickness	Ulcerative Status
T_X	Primary tumor cannot be addressed (eg, shave biopsy)	
T_0	No evidence of primary tumor	
T_{is}	Melanoma in situ	
T_1	≤1 mm	Unknown or unspecified
	0.8-1 mm	With or without ulceration
	<0.8 mm	A: Without ulceration B: With ulceration
T_2	>1-2 mm	Unknown or unspecified A: Without ulceration B: With ulceration
T_3	>2-4 mm	Unknown or unspecified A: Without ulceration B: With ulceration

T_4	>4 mm	Unknown or unspecified A: Without ulceration B: With ulceration
N Classification	**No. of Tumor Involved Nodes**	**Presence of In-Transit, Satellite, and/or Microsatellite Metastases**
N_X	Regional lymph nodes cannot be assessed	No
N_0	No regional lymph nodes	No
N_1	1 node	
N_{1a}	1 clinically occult node[a]	No
N_{1b}	1 clinically detected node	No
N_{1c}	No regional lymph node disease	Yes
N_2	2-3 nodes	
N_{2a}	2-3 clinically occult nodes	No
N_{2b}	2-3, with 1 clinically detected node	No
N_{2c}	1 clinically occult or detected node	Yes
N_3	≥4 nodes	
N_{3a}	≥4 clinically occult nodes	No
N_{3b}	≥4, with 1 clinically detected, or presence of any matted nodes	No
N_{3c}	≥2 clinically occult or detected and/or any matted nodes	Yes
M Classification	**Site**	**Serum Lactate Dehydrogenase**
M_0	No detectable distant metastasis	
M_{1a}	Distant skin, soft tissue, and/or nonregional lymph nodes	Not elevated Elevated: $M_{1a(1)}$
M_{1b}	Lung metastases	Not elevated Elevated: $M_{1b(1)}$
M_{1c}	Any distant metastasis visceral metastases	Not elevated Elevated: $M_{1c(1)}$

M_{1d}	Distant metastases to the CNS	Not elevated Elevated: $M_{1d(1)}$

M, metastasis; N, node; T, tumor.

[a]Clinically occult node detected by sentinel lymph node biopsy.

Data from Reference 17.

TABLE 162-5

American Joint Committee on Cancer Tumor (T), Node (N), Metastasis (M) Stage Grouping for Cutaneous Melanoma

Pathologic Stage	T	N	M	Clinical Stage	T	N	M
0	T_{is}	N_0	M_0	0	T_{is}	N_0	M_0
IA	T_{1a}	N_0	M_0	IA	T_{1a}	N_0	M_0
	T_{1b}	N_0	M_0	IB	T_{1b} T_{2a}	N_0 N_0	M_0 M_0
IB	T_{2a}	N_0	M_0				
IIA	T_{2b}	N_0	M_0				
	T_{3a}	N_0	M_0	IIA	T_{2b}	N_0	M_0
IIB	T_{3b}	N_0	M_0		T_{3a}	N_0	M_0
	T_{4a}	N_0	M_0	IIB	T_{3b}	N_0	M_0
	T_{4a}	N_0	M_0		T_{4a}	N_0	M_0
IIC	T_{4b}	N_0	M_0	IIC	T_{4b}	N_0	M_0
IIIA	$T_{1a/b}$, T_{2a}	N_{1a}, N_{2a}	M_0	III	Any T, T_{is}	$>N_1$	M_0
IIIB	T_0	N_{1b}, N_{1c}	M_0				
	$T_{1a/b}$, T_{2a}	$N_{2b/c}$, N_{2b}	M_0				
	T_{2b}, T_{3a}	N_{1a-c}, $N_{2a/b}$					
IIIC	T_0	$N_{2b/c}$, $N_{3b/c}$	M_0				
	T_{1a}-T_{3a}	N_{2c}, N_{3a-c}	M_0				
	T_{3b}, T_{4a}	Any N ≥ N_1	M_0				
	T_{4b}	N_{1a-c}-N_{2a-c}	M_0				
IIID	T_{4b}	N_{3a-c}	M_0				
IV	Any T, T_{is}	Any N	M_1	IV	Any T	Any N	M_1

As with other solid tumors, regional lymph node involvement is a powerful predictor of tumor burden and patient outcome. Sentinel lymph node

biopsy (SLNB) is a minimally invasive procedure that determines if a patient is a candidate for a complete lymph node dissection. The rationale for lymphatic mapping and subsequent SLNB is based on the observation that skin regions have patterns of lymphatic drainage to specific lymph nodes in the regional lymphatic basin. The sentinel lymph node is the first node in the lymphatic basin into which the primary melanoma drains. Unlike other solid tumors, melanoma progresses in an orderly nodal distribution. SLNB allows for the detection of micrometastases with a more thorough examination of a single sentinel node than is possible when examining multiple lymph nodes with a lymph node dissection. SLNB is associated with low false-negative rates and low complication rates.[18] SLNB may be most useful for melanomas located in ambiguous drainage sites such as the head and neck. Detection of clinically undetectable disease in a lymph node basin not directly adjacent to the primary lesion may allow for upstaging of patients who initially are believed to have node-negative disease. The American Society of Clinical Oncology and Society of Surgical Oncology joint clinical practice guidelines recommend SLNB for patients with any intermediate-thickness melanoma and may be considered for a thinner melanoma.[18]

Tumor thickness, ulceration, and mitotic rate, in addition to age and gender, are the primary indicators of the natural history of the disease and correlate with prognosis. Mitotic rate, defined as the number of mitosis per square millimeter, is an important prognostic factor for developing metastatic disease. Increasing mitotic rate, characterized as greater than ≥1 mitosis/mm^2, represents a more aggressive lesion and is associated with a poorer survival rate. Other factors such as tumor growth pattern, vertical growth phase, histological subtype, density of tumor-infiltrating lymphocytes (TILs) in the tumor tissue, elevated LDH level, satellite lesions, and angiolymphatic invasion may be associated with survival.[19] The location of the primary tumor on the skin is also important as tumors of the extremities have increased survival compared with those with axial, neck, head, and trunk tumors. In addition, several additional prognostic factors have been identified in patients with advanced disease. The number of metastatic sites, involvement of the central nervous system, gastrointestinal tract, liver, pleura, or lung, Eastern Cooperative Oncology Group (ECOG) performance status of 1 or greater, male sex, and prior immunotherapy have all been associated with poor prognosis.[8]

TREATMENT

Desired Outcomes

Treatment of cutaneous melanoma depends on the stage of disease. Localized disease is managed, and often cured, with surgical ablation. Regional disease is treated with surgical resection of the primary lesion and, depending on the risk of recurrence, adjuvant therapy to eradicate any residual disease and cure the patient. The role of ipilimumab as adjuvant therapy after surgical resection is limited with combination BRAF and MEK inhibitors and PD-1 inhibitors now favored in this setting based on recent FDA approvals. Historically, metastatic melanoma has been a difficult disease to treat. The goals of treatment for metastatic disease are to slow tumor progression, prolong survival, relieve acute symptoms, and improve quality of life. After decades of poor treatment options, several effective treatment options are now available, including targeted agents (BRAF and MEK inhibitors) and immunotherapy (CTLA-4 and PD-1 inhibitors) approved to treat metastatic melanoma. Targeted agents offer rapid and high-response rates with prolonged time-to-disease progression, while immunotherapy can induce durable responses. These new treatment options have increased survival expectations to an all-time high in the history of melanoma treatment. As a result of the differences in the underlying pathophysiology and treatment of uveal melanoma, the NCCN developed disease-specific guidelines.[20]

Surgery

Patients who present with a suspicious pigmented lesion should undergo a full-thickness excisional biopsy, if possible. A full-thickness incisional or punch biopsy is preferred in cases where an excisional biopsy is not possible, to provide microstaging and ultimately determine therapy.

2 Localized cutaneous melanoma can often be cured with surgical excision. The cure rates for melanomas smaller than 1 mm are as high as 98%.[21] The extent of the excision margin determines the risk of local recurrence and ultimately survival. For melanoma in situ, excision of the visible lesion or biopsy site with a 0.5- to 1 cm border of clinically normal skin and a layer of subcutaneous tissue along with confirmation of histologically negative peripheral margins is recommended. The recommended clinical margin for invasive melanoma depends on tumor thickness. Excision with a 1-cm margin of clinically normal skin and underlying subcutaneous tissue is recommended for invasive melanomas 1 mm thick or smaller. Current guidelines recommend a 1 to 2 cm margin for melanoma with a tumor thickness of 1.01 to 2 mm.[8] Lesions that are 2 to 4 mm thick should be excised with a 2 cm margin and primary tumors more than 4 mm thick require at least a 2 cm margin. Surgical management of lentigo maligna melanoma is problematic as subclinical extension of atypical junctional melanocytic hyperplasia may extend beyond the visible margins. Complete excision of these

lesions is important.

When isolated regional lymph nodes in the absence of distant disease are detected via physical examination, a therapeutic lymphadenectomy is recommended. Neoadjuvant therapy should also be considered in patients at high risk of perioperative morbidity or if gross complete resection of nodal disease may not be achieved. The extent of the therapeutic lymph node dissection is often modified according to the anatomic area of the lymphadenopathy. Selective regional lymphadenectomy performed after scintigraphic and dye lymphographic identification of the affected draining sentinel lymph node(s) is the standard of care for melanomas more than 1 mm thick. If the lesion is less than 0.8 mm in thickness with ulceration, 0.8 to 1 mm in thickness with or without ulceration, or <0.8 mm with other adverse features (very high mitotic index >2/mm^2 or lymphovascular invasion), lymphatic mapping with SLNB should be discussed and considered. If the sentinel node is found to have micrometastatic melanoma, regional dissection of the involved nodal basin is performed. The likelihood of detecting metastatic disease in the sentinel lymph node is <5% in thin melanomas that are less than 0.8 mm, but increases to more than 30% in tumors 4 mm thick.[22] The Multicenter Selective Lymphadenectomy Trial (MSLT-1) investigated the use of SLNB and immediate complete lymph node dissection (CLND) compared to nodal observation in patients with melanoma undergoing a wide local excision. Results showed a significant improvement in disease-free survival but not melanoma-specific survival, supporting the staging value of SLNB.[23] The Multicenter Selective Lymphadenectomy Trial II (MSLT-II) then randomized sentinel lymph node-positive patients to either CLND or nodal observation. No difference in melanoma-specific survival was observed despite an increased rate of regional disease control.[24] As a result, the value of CLND in routine practice remains unclear, with nodal basin ultrasound surveillance preferred for patients without clinically positive nodes.[8] However, SLNB results are important for accurate staging and aid in the decision to offer adjuvant treatment.[22]

One of the most important aspects of surgical management for cutaneous melanoma is patient follow-up. Postsurgical follow-up of patients who have had a melanoma excised is essential to monitor for undetected metastatic disease and the development of a second primary cutaneous melanoma or nonmelanoma malignancy. Scheduled screening, in addition to routine surgical follow-up, is required for any patient with a melanoma; the recommended frequency and duration depend on the stage of melanoma. The optimal duration of follow-up remains controversial. Most patients who develop recurrent disease do so within the first 5 years after treatment but late recurrences (more than 10 years after surgery) have been observed. The increased lifetime risk of developing a second primary melanoma supports lifetime dermatologic surveillance for all patients.[8]

A patient with stage III melanoma typically has lymph node involvement but intralymphatic metastases, including satellite metastases and in-transit metastases, may also occur. Satellite metastases are either clinically (visible) or pathologically (microscopic) detectable and occur within 2 cm of the primary site. In-transit metastases are defined as regional metastases that occur more than 2 cm from the original lesion and are more common in individuals with thick, ulcerated lesions.[8] Surgery may be used to manage in-transit lesions with the goal of complete resection with clear margins. Unfortunately, surgery is not always feasible and subsequent recurrence in the same extremity often occurs after initial resection of an in-transit metastasis.

The role of surgery beyond that of cure is less clear, although surgery may offer palliation for patients with isolated metastasis.[22] Brain metastases occur in up to 50% of patients with metastatic melanoma. Surgical resection, with or without radiation, has been used in select individuals. High control rates of brain metastasis have been achieved with focal radiation therapy such as linear accelerator–based stereotactic radiosurgery or gamma-knife technologies.[8] Surgical resection or bypass may also offer significant symptom relief to patients with a bowel obstruction due to metastasis. Despite the lack of controlled clinical trials, the impact of palliative surgery should be evaluated in the context of a patient's comfort and quality of life. Surgery may improve quality of life, result in long-term disease control, and extend survival in select patients with metastatic disease.[22]

Adjuvant Therapy

3 The risk of relapse and death after resection of a local or regional cutaneous melanoma is the primary determinant for the use of adjuvant therapy. Adjuvant trials have focused on patients at intermediate or high risk for recurrence.

Historically, melanoma has shown resistance to traditional treatment modalities such as radiation and chemotherapy. However, melanoma is considered one of the most immunogenic solid tumors and lymphocyte infiltration in the tumor suggests that immunomodulation may impact the biology of the disease. Early work with nonspecific immunomodulators, such as levamisole and Bacillus Calmette-Guérin (BCG), resulted in tumor regression but many of these responses were limited and short-lived. The use of adjuvant immunotherapy to treat these patients has been investigated to prevent distant recurrence and improve long-term survival.

CTLA-4 Inhibitor

It is well known that T cells play a crucial role in cell-mediated immunity. They are activated when the T-cell receptor (TCR) binds to its antigen in conjunction with the binding of CD28 on the T cell to the costimulatory molecule B7 on antigen-presenting cells (APCs). To prevent over activation of T cells, immune checkpoints such as CTLA-4 function as inhibitory receptors for the costimulatory molecule B7. Crosslinking of CTLA-4 by B7 inhibits T-cell activation, transcription, translation, and transduction. CTLA-4 blockade overcomes this inhibition and results in the activation and proliferation of T cells.[11] Ipilimumab, a monoclonal antibody against CTLA-4, has efficacy in both the adjuvant and metastatic setting in the treatment of melanoma. The EORTC 18071 trial evaluated 475 patients treated with high-dose ipilimumab as compared to placebo in the adjuvant setting. Median recurrence-free survival was longer in patients treated with high-dose ipilimumab as compared with placebo (26.1 vs 17.1 months). Long-term data demonstrated significantly higher 5-year recurrence-free and overall survival with adjuvant ipilimumab as compared to placebo.[25]

However, these results did not come without toxicity. CTLA-4 inhibitors produce immune-related adverse events (irAEs) that are distinct and different from adverse drug reactions associated with conventional cancer treatments (see Table 162-6). irAEs are the result of the activation of self-reactive T cells. The incidence of irAEs with the high-dose ipilimumab in EORTC 18071 was 90% and up to 55% of patients experienced grade 3 or 4 irAEs.[25] The most common serious irAEs observed in the EORTC 18071 adjuvant trial were autoimmune colitis and autoimmune hepatitis. Autoimmune endocrinopathies occurred at a higher frequency than in the metastatic disease trials. irAEs led to treatment discontinuation in 52% of patients treated with ipilimumab. Of concern, five deaths were attributed to adverse drug reactions.[25]

TABLE 162-6

Management of Immune-Related Adverse Effects (irAEs)

Organ Toxicity	Signs/Symptoms	Management	Comments
Skin and Mucosa	Pruritus, rash, desquamation, mucositis	Grade 1 Topical corticosteroids (betamethasone 0.1%) Urea-based creams Oral antipruritic as needed (diphenhydramine or hydroxyzine) Grade 2 Moderate-high potency topical corticosteroids If unresponsive to topical, consider prednisone 0.5 mg/kg/day Oral antipruritic as needed (diphenhydramine or hydroxyzine) Grade 3 or 4 Hold therapy High-potency topical corticosteroids to affected areas Prednisone 0.5-1 mg/kg/day or equivalent (increase up to 2 mg/kg/day if no improvement) Consider inpatient care	Rare cases of toxic epidermal necrosis and Stevens–Johnson syndrome have been reported. Permanent discontinuation of immunotherapy is warranted in these cases.
Gastrointestinal	Diarrhea, hematochezia,	Grade 1 Consider holding treatment	Infliximab 5 mg/kg IV may be given if symptoms do not improve with 48-72 hours of high-dose

	abdominal cramping, nausea, and vomiting	Oral hydration/electrolyte repletion Close monitoring Loperamide or diphenoxylate hydrochloride Grade 2 Hold immunotherapy Prednisone/methylprednisolone 1-2 mg/kg/day No response in 2-3 days, consider adding infliximab or vedolizumab Grade 3 or 4 Consider inpatient care Methylprednisolone 1-2 mg/kg/day No response in 1-2 days, add infliximab or vedolizumab	steroids. Bowel perforation and obstruction may occur in cases of severe colitis.
Hepatic	Transaminitis, jaundice, sclera icterus	Grade 1 Consider holding therapy Increase lab monitoring Grade 2 Hold therapy Monitor liver function tests every 3-5 days Consider prednisone 0.5-1 mg/kg/day Grade 3 Hold treatment Prednisone 1-2 mg/kg/day or equivalent No response in 1-2 days, consider adding mycophenolate Grade 4 Permanently discontinue treatment Prednisone/methylprednisolone 1-2 mg/kg/day or equivalent Inpatient care Monitor liver enzymes daily	Mycophenolate mofetil 500 mg IV/PO every 12 hours can be used in patients who do not respond to steroids within 48 hours. Avoid infliximab in hepatitis.
Neurologic	Muscle weakness, motor neuropathies, sensory neuropathies	Grade 1-2 Consider holding treatment Monitor Grade 3 or 4 Inpatient care Permanently discontinue treatment Methylprednisolone 1-2 mg/kg/day Prednisone if severe or progressing symptoms, consider pulse steroids methylprednisolone 1 g IV daily × 3-	Rare case reports of Guillain–Barre' syndrome and myasthenia gravis have been reported with ipilimumab.

		5 days plus IVIG or plasmapheresis	
Endocrine	Headache, weakness, visual changes, behavioral changes, electrolyte imbalances	Grade 1 or 2 Appropriate hormone replacement therapy Endocrine consultation Grade 3 or 4 Hold therapy until acute symptoms resolve Carefully consider high-dose steroids for acute severe symptoms	Potential endocrinopathies include Addison's disease, pan-hypopituitarism, adrenal crisis, and hypophysitis. These effects may be permanent.
Ocular	Photophobia, eye dryness, blurred vision	Grade 1 or 2 Consider holding treatment Prednisolone acetate 1% topical Grade 3 or 4 Hold treatment Ophthalmic and systemic prednisone/methylprednisolone	Rare cases of episcleritis and uveitis have been reported.
Pulmonary	Dyspnea, new or worsened cough, chest pain, hemoptysis	Grade 1 Consider holding treatment Consider chest CT with contrast Grade 2 Hold treatment Consider infectious workup Prednisone 1-2 mg/kg/day or equivalent If no improvement after 2-3 days, treat as Grade 3 Grade 3 or 4 Permanently discontinue treatment Methylprednisolone 1-2 mg/kg IV then 1-2 mg/kg/day of oral prednisone or equivalent If no improvement after 2 days, consider adding infliximab, IVIG, or mycophenolate	Pneumonitis is more common with pembrolizumab and nivolumab than ipilimumab.

Data from Reference 26.

The incidence of irAEs with ipilimumab are dose related and tend to follow a pattern: skin-related toxicities typically occur after the first dose; colitis tends to occur after the second dose; and hepatitis and endocrinopathies often occur after the third or fourth dose.[27] However, irAEs can occur at any time during treatment and even after the treatment is discontinued. Their development cannot be predicted because they result from the individual's immune system and not the treatment itself. Most irAEs are reversible with treatment and resolve after 6 to 8 weeks; the exception being endocrinopathies which may require lifelong hormonal treatment. Close monitoring and early intervention are necessary for effective management of

irAEs while on therapy.[8] It is recommended that patients obtain a comprehensive metabolic panel (with liver function tests), complete blood count, and thyroid function tests at baseline, throughout treatment and for up to 6 months after treatment.[26,27]

Ipilimumab therapy should be held and high-dose systemic corticosteroids initiated for grade 2 irAEs that do not improve from withholding therapy or for any grade 3 or 4 irAE. Consideration may be given to restart ipilimumab after an irAE improves to grade 0 or 1 and systemic corticosteroid dose is less than or equal to prednisone 10 mg per day. In early studies, corticosteroids were discouraged due to the theoretical risk of blunting the desired immune response. However, the efficacy of ipilimumab is not compromised when corticosteroids are given for toxicity management.[26] For patients who develop steroid-refractory irAEs, defined as no response to high-dose steroids within 48 to 72 hours of initiation, other immunosuppressive agents have been used in addition to corticosteroids. For example, infliximab and mycophenolate have been used as secondary immunosuppressants for patients who develop steroid-refractory colitis and hepatitis, respectively. Due to case reports of hepatotoxicity with infliximab, this agent should be avoided in patients with autoimmune hepatitis. Published guidelines for the treatment of irAEs are available.[26] In cases of severe or life-threatening irAEs, permanent discontinuation of ipilimumab therapy is recommended. In clinical studies reported to date, patients who experienced grade 3 or 4 autoimmune toxicities were also the most likely to exhibit tumor regression and increased time to relapse in the metastatic setting.[26]

PD-1 Inhibitors

Physiologically, the binding of PD-1 to its ligand (PD-L1 or PD-L2) results in an inhibitory signal to suppress T-cell activation, therefore preventing autoimmunity and recognition of self. However, melanoma cells can overexpress PD-L1, leading to T-cell exhaustion and the inability to mount an immune response against a tumor. Monoclonal antibodies directed against PD-1 block the binding of PD-L1, thus allowing T cells to remain stimulated.[7] PD-1 inhibitors have exhibited improved efficacy and reduced toxicity compared to ipilimumab.

Pembrolizumab and nivolumab are PD-1 inhibitors initially approved for the treatment of metastatic melanoma that have been evaluated in the adjuvant setting. Checkmate-238 was the first in a series of published adjuvant studies that changed the treatment landscape of early-stage melanoma. A total of 906 patients with high-risk stage III or stage IV melanoma who underwent complete resection were randomized to receive either ipilimumab 10 mg/kg IV every 3 weeks for four doses then every 12 weeks or nivolumab 3 mg/kg IV every 2 weeks for up to 1 year. Results showed 1-year recurrence-free survival of 70.5% with nivolumab as compared to 60.8% with ipilimumab.[28] The risk of grade 3 to 4 toxicities was significantly lower in the patients receiving nivolumab (14.4%) versus ipilimumab (45.9%). Treatment discontinuation due to an adverse drug reaction occurred in 9.7% of patients treated with nivolumab versus 42.6% of patients treated with ipilimumab.[28] With longer follow-up, nivolumab has demonstrated a sustained recurrence-free survival benefit over ipilimumab. However, fewer deaths than anticipated occurred and 4-year overall survival was similar in both groups.[29] Based on these results, nivolumab is an efficacious adjuvant treatment with less toxicity than ipilimumab.

A similar study of adjuvant pembrolizumab, Keynote-054, was conducted in patients with stage III melanoma undergoing complete resection. Patients were randomized to receive pembrolizumab 200 mg IV every 3 weeks or placebo for up to 1 year. The 1-year recurrence-free survival rate was 75.4% with pembrolizumab compared to 61.0% with placebo. Grade 3 to 4 adverse drug reactions were reported in 14.7% of patients who received pembrolizumab.[30] Based on these two studies, PD-1 inhibitors are now considered the standard of care for the adjuvant treatment of melanoma in patients with stage III disease who have undergone complete resection.[8]

With significant benefit seen in stage III melanoma, adjuvant treatment with PD-1 inhibitors has been studied in patients with high-risk stage II disease. KEYNOTE-716 was a multicenter, randomized, double-blind, placebo-controlled trial that randomized patients with fully resected stage IIB or IIC melanoma to receive either pembrolizumab 200 mg every 3 weeks or placebo for up to 1 year. At a median follow-up of 14.4 months, this study showed a significant improvement in recurrence-free survival, with a 35% reduction in risk in those who received pembrolizumab compared to placebo.[31] Although further follow-up is needed to evaluate if there is an overall survival benefit, the FDA approved pembrolizumab for the adjuvant treatment of patients with stage IIB or IIC melanoma following complete resection based on this data. This approval supports the introduction of immunotherapy, specifically PD-1 inhibitors, in the adjuvant setting due to their ability to reduce the risk of melanoma recurrence and their favorable toxicity profile.

Targeted Therapy

Mutations in BRAF, found in up to 50% of melanomas, lead to the constitutive activation of the MAPK pathway and uncontrolled cell growth/differentiation.[7] BRAF-targeted therapies have shown an improvement in survival in patients with metastatic melanoma. However, resistance

eventually develops, potentially caused by mutations in MEK. The use of MEK inhibitors in combination with BRAF inhibitors delays the development of acquired resistance and increases efficacy in the metastatic setting.

For patients with early-stage melanoma and molecular mutations identified in BRAF, the combination of BRAF and MEK inhibitors has been studied in the adjuvant setting. The COMBI-AD trial investigated the use of adjuvant dabrafenib and trametinib in patients with completely resected, stage III melanoma, and the presence of a *BRAF* V600E or V600K mutation. Patients were randomized to receive dabrafenib 150 mg twice daily plus trametinib 2 mg daily or placebo for up to 1 year. The 3-year relapse-free survival rate was 58% in the dabrafenib/trametinib group and 39% in the placebo group, with a 53% lower risk of relapse at 2.8 years.[32] Overall survival was also increased in the combination arm but this did not reach statistical significance in the first interim analysis. No new or unexpected adverse drug reactions were observed in the adjuvant setting. Relapse-free survival at 5 years was 52% in patients treated with dabrafenib and trametinib versus 36% with placebo and no long-term adverse drug reactions were seen.[33] The major toxicities of BRAF and MEK inhibitor therapy will be discussed in the Treatment of Metastatic Melanoma section. Based on this data, the combination of dabrafenib and trametinib received FDA approval for adjuvant treatment in patients with stage III melanoma and the presence of a *BRAF* V600E or V600K mutation following complete resection.

Summary of Adjuvant Therapy

High-dose ipilimumab is a treatment option for patients with high-risk disease, but it has fallen out of favor because of its toxicities and has been removed from the list of recommended adjuvant treatment options in the NCCN guidelines. The treatment of choice in this setting is PD-1 inhibitors (nivolumab or pembrolizumab) or dabrafenib and trametinib for patients with BRAF V600-activating mutation due to improved efficacy and reduced toxicity.[8]

Treatment of Metastatic Melanoma

Chemotherapy and Biochemotherapy

4 Although many chemotherapy drugs show in vitro activity against melanoma, only a few have consistently shown a response rate greater than 10% in individuals with metastatic melanoma. Dacarbazine and temozolomide, the oral prodrug of the active metabolite of dacarbazine, are alkylating agents that have been studied in the treatment of metastatic melanoma. Dacarbazine is the only FDA-approved chemotherapeutic agent for treatment in this setting and once was considered the standard of care. Reported response rates with these two cytotoxic drugs are 10% to 25%, with an average duration of response of 5 to 7 months.[8] Common adverse drug reactions include myelosuppression and severe nausea and vomiting. Carboplatin in combination with paclitaxel demonstrated activity in the second-line setting.[34] Response rates of 15% to 17% were seen in trials with single-agent paclitaxel.[8] A phase III trial comparing albumin-bound paclitaxel with dacarbazine in chemotherapy-naïve melanoma patients reported an increase in progression-free survival and a trend in overall survival in patients receiving albumin-bound paclitaxel. Neuropathy and neutropenia were more common in the albumin-bound paclitaxel arm.[35] The NCCN guidelines state that these chemotherapy agents should not be routinely used because of their lack of overall survival benefit and toxicity and should only be considered for patients who are not candidates for immunotherapy or targeted therapy.[8]

To improve the low response rates with chemotherapy, the strategy of combining chemotherapy (dacarbazine, platinum agents, or vinca alkaloids) and cytokines (aldesleukin or interferon), often termed biochemotherapy, has been evaluated for the management of metastatic melanoma as well as the adjuvant setting. The primary rationale for this combination is to increase overall activity and response rates based on preclinical work suggesting potential synergistic interactions between cytokines and some chemotherapy agents. Results of clinical studies with biochemotherapy have not demonstrated a clear survival advantage and toxicities are additive and can be severe. The NCCN guidelines do not recommend biochemotherapy in the adjuvant or metastatic setting.[8]

Immunotherapy

Significant attention has been given to immunotherapy as a treatment option in metastatic melanoma due to its general resistance to traditional treatment modalities. Over the past decade, advances in immunotherapy for the treatment of melanoma have improved survival in patients with metastatic disease.

Interleukin-2

Interleukin-2 is a glycoprotein produced by activated lymphocytes. IL-2 was first identified as a T-cell growth factor, but IL-2 is also a growth factor for various cells, including lymphocytes and natural killer (NK) cells. The precise mechanism of cytotoxicity of IL-2 is unknown. In vitro and in vivo, IL-2 stimulates the production and release of many secondary monocyte-derived and T-cell–derived cytokines, including IL-4, IL-5, IL-6, IL-8, tumor necrosis factor (TNF)-α, granulocyte-macrophage colony-stimulating factor, and IFN-γ, which may have direct or indirect antitumor activity. In addition, IL-2 stimulates the cytotoxic activities of NK cells, monocytes, lymphokine-activated killer (LAK) cells, and cytotoxic T lymphocytes (CTLs). IL-2 also activates endothelial cells, which results in increased expression of adhesion molecules.[36]

High-dose IL-2, as known as aldesleukin, was evaluated in a series of trials with objective response rates around 16%. Of significance, 6% of those patients exhibited durable complete responses (median response, 70 months).[36] Responses were seen in various metastatic sites such as the lung, liver, bone, lymph nodes, and subcutaneous tissue. The FDA-approved high-dose aldesleukin regimen for the treatment of metastatic melanoma is 600,000 IU/kg/dose every 8 hours for a maximum of 14 doses in a 5-day period given for two cycles, with a 10- to 14-day rest period between cycles. At these doses, cytokine-induced capillary leak syndrome is a common problem and often is accompanied by significant hypotension, visceral edema, dyspnea, tachycardia, and arrhythmias. Increased permeability of capillary walls allows for a fluid shift from the intravascular space into tissues. Hypotension may occur as the patient becomes intravascularly dehydrated, resulting in reflex tachycardia and arrhythmias. In addition, the decrease in blood volume may result in decreased renal blood flow, manifesting as increases in blood urea nitrogen, serum creatinine, edema, and weight gain, and a decrease in urine output (input greater than output). Visceral edema may result in pulmonary congestion, pleural effusions, and edema. The management of patients receiving high-dose aldesleukin requires extensive supportive care medications, careful monitoring, and staff trained in aspects of critical care such as hypotension management. Constitutional symptoms are a frequent complication of aldesleukin therapy and become more intense as therapy progresses. Additional adverse drug reactions of aldesleukin include pruritus, eosinophilia, bone marrow suppression, increased liver function tests, neurologic disturbances, diarrhea, and nausea.[8]

Careful patient selection for aldesleukin therapy is important. Pretreatment factors such as performance status, site of metastasis, and LDH may predict who will respond. Based on reports of long-term responses (>10 years) experienced by some patients, the benefit certainly exceeds the risk for those individuals. Unfortunately, it is difficult to determine which individuals will respond to aldesleukin therapy because no biologic or immunologic biomarkers have been found to correlate with response. The decision to treat an individual with high-dose aldesleukin should be based on an analysis of an individual patient's risk versus potential benefit. With newer agents now available on the market, and its complexity of administration, the role of aldesleukin has diminished.[8]

CTLA-4 Inhibitors

5 CTLA-4 was the first immune checkpoint identified as a target for immunotherapy and ipilimumab was the first drug in this class to demonstrate efficacy in metastatic melanoma. Results from phase I and II trials with ipilimumab demonstrate up to 20% response rates in advanced disease.[8] In a phase III trial of 676 HLA-A*0201-positive patients with refractory metastatic melanoma, ipilimumab (3 mg/kg) plus a glycoprotein 100 (gp100) peptide vaccine was compared with ipilimumab (3 mg/kg) alone or gp100 alone.[8] The median overall survival time was significantly longer in patients treated with ipilimumab, alone or combined with gp100, as compared with patients treated with gp100 alone. Another phase III trial compared a higher dose of ipilimumab (10 mg/kg) plus dacarbazine with dacarbazine alone in patients previously untreated for metastatic melanoma. Ipilimumab plus dacarbazine demonstrated significantly longer median overall survival and higher survival rates at 1 year (47.3% vs 36.3%), 2 years (28.5% vs 17.9%), and 3 years (20.8% vs 12.2%) than dacarbazine alone.[8] Based on these results, ipilimumab, dosed at 3 mg/kg IV every 3 weeks for four doses became the first FDA-approved drug for the treatment of unresectable or metastatic melanoma with a survival benefit. With longer follow-up, the survival benefit was maintained in patients who had an initial response to ipilimumab. Five-year follow-up data demonstrate survival rates of 13% to 23% with survival durations of 13 to 16 months.[37] It is also important to note that the 3-year survival mark is noteworthy for patients treated with ipilimumab. Up to 85% of the patients who were alive at 3 years were alive at 4 years, suggesting that the 3-year survival mark may be a useful surrogate endpoint.[38] After a period of time, it is felt that the balance between immune response and tumor growth can shift leading to disease relapse after an extended duration of response. Retreatment can be an option for patients who had an initial clinical benefit and has been shown to re-induce a response; no additional toxicities have been observed with re-induction.[34]

One of the greatest lessons learned from early clinical trials with ipilimumab was the difference in the kinetics of response seen with immunotherapies

and how to evaluate response to treatment. Patients have no regression of disease for many weeks after treatment initiation. Even more alarming was around 10% of patients initially experienced a significant increase in tumor burden which suggested disease progression. This pseudoprogression was then followed by a delayed response to the drug after about 12 weeks of therapy; some patients continued to have a steady reduction in tumor burden over time which eventually produced a durable clinical benefit. It is hypothesized that the delayed response is related to the time needed to stimulate the immune system.[37] Due to this phenomenon, the Response Evaluation Criteria in Solid Tumors (RECIST) has developed immune-related response criteria (irRECIST) to evaluate response to immunotherapies.[39]

6 The greatest challenge with the use of ipilimumab is the management of irAEs. Patients must be thoroughly educated on signs and symptoms of irAEs and when to seek medical attention. Clinicians should be familiar with the different types, timing, and appropriate management of irAEs (see Table 162-6). As previously discussed, management of irAEs should follow established treatment guidelines.[26]

PD-1 Inhibitors

5 As the next generation of immune checkpoint inhibitors, these agents have demonstrated response rates of up to 40% in metastatic melanoma with long-term clinical benefit seen in early phase I trials.[40] It became clear that PD-1 inhibitors have a more favorable safety profile with significantly fewer irAEs compared to ipilimumab. Additionally, clinical benefit was seen in patients who had previously been treated with ipilimumab. The KEYNOTE-001 trial evaluated the efficacy of pembrolizumab in patients who were previously treated with ipilimumab. The trial reported an overall response rate of 26%, progression-free survival of 45% at 24 weeks, and 1-year overall survival of 58%.[41] Treatment was well tolerated with grade 3 or 4 adverse events occurring in 12% of patients. In the CheckMate 037 randomized controlled trial of patients previously treated with ipilimumab, nivolumab produced higher response rates (32% vs 11%) with fewer irAEs when compared to chemotherapy.[42] An important observation from these studies is the lack of cross-resistance between ipilimumab and PD-1 inhibitors. As with ipilimumab, if patients are able to achieve a response to these agents, that response can be maintained for an extended duration. Both pembrolizumab 2 mg/kg IV every 3 weeks and nivolumab 3 mg/kg IV every 2 weeks were approved to treat patients with advanced or unresectable melanoma who progressed on previous ipilimumab therapy and, if applicable, a BRAF inhibitor. Each agent has received FDA approval for flat dosing (pembrolizumab 200 mg every 3 weeks or 400 mg every 6 weeks; nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks) based on dose/exposure, efficacy, and safety data.

6 Like ipilimumab, the response to PD-1 inhibitors is delayed but the response to PD-1 inhibitors may be slightly faster than with ipilimumab. The irAE profile with PD-1 inhibitors is different, with the most common adverse drug reactions with pembrolizumab and nivolumab being fatigue, cough, nausea, pruritus, rash, decreased appetite, constipation, arthralgias, and diarrhea.[41,42] The risk of grade 3 or 4 irAEs is significantly lower as compared to ipilimumab. Specifically, the incidence of grade 3 or 4 diarrhea/colitis with PD-1 inhibitors is dramatically lower and occurs in only 1% to 2% of patients. However, a higher incidence of autoimmune pneumonitis (1%-2%) is seen with nivolumab and pembrolizumab as compared to ipilimumab.[27] Patients should be counseled to notify a clinician if they notice new or worsening cough, chest pain, or shortness of breath. Treatment of irAEs follows the same established treatment algorithms as ipilimumab (Table 162-6).

First-line therapy with PD-1 inhibitors has been evaluated to treat unresectable or metastatic melanoma. In the KEYNOTE-006 trial, pembrolizumab was compared directly to ipilimumab for first-line treatment. In this trial, 834 patients with unresectable or metastatic melanoma were randomized to receive pembrolizumab 10 mg/kg every 2 weeks or every 3 weeks or ipilimumab 3 mg/kg every 3 weeks for four doses. One-year overall survival rates were 75% for the pembrolizumab every 2 weeks, 68.4% for the pembrolizumab every 3 weeks, and 58.2% for ipilimumab.[43] Treatment-related grade 3 or 4 adverse effects were lower in both pembrolizumab arms. With better efficacy and less toxicity compared to ipilimumab, the FDA-approved pembrolizumab 2 mg/kg IV every 3 weeks as a first-line treatment option for metastatic melanoma. Similarly, in a randomized controlled trial comparing nivolumab with dacarbazine for first-line treatment of BRAF wild-type metastatic melanoma, nivolumab produced significantly better 1-year overall survival rates, median progression-free survival, and overall response rates.[44] The NCCN Guidelines recommend both pembrolizumab and nivolumab as preferred first-line treatment options for patients with unresectable or metastatic disease.[8]

Combination CTLA-4 and PD-1 Inhibitors

5 6 The combination of a CTLA-4 inhibitor, which stimulates the immune system at the central level in the priming phase of T-cell activation and proliferation, and a PD-1 inhibitor, which acts in the peripheral phase within the tumor microenvironment, can result in synergistic activity. Survival

rates of 90% at 1 year and >80% at 2 years were unprecedented in the treatment of metastatic melanoma in early trials.[8] This combination was studied in the landmark Checkmate-067 trial, which included 945 previously untreated patients with unresectable stage III or IV melanoma. Patients were randomized to receive either nivolumab 3 mg/kg alone, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, or ipilimumab 3 mg/kg alone. The median progression-free survival was 11.5 months with nivolumab plus ipilimumab, compared with 6.9 months with nivolumab alone and 2.9 months with ipilimumab alone.[45] After 6.5 years of follow-up, the median overall survival with the combination is 72.1 months, 36.9 months with nivolumab alone, and 19.9 months with ipilimumab alone.[46] Of particular importance, 81% of patients who received the combination were off treatment and never received subsequent systemic therapy, highlighting the durability of treatment responses. A second trial, CheckMate-069, confirmed the benefits of this combination. In this double-blind, randomized, controlled trial, 142 untreated melanoma patients were randomized to receive ipilimumab 3 mg/kg plus nivolumab 1 mg/kg or the same dose of ipilimumab with placebo once every 3 weeks for four doses. Patients then received nivolumab (ipilimumab arm) or placebo at the same dose every 2 weeks until disease progression or unacceptable toxicity.[47] The objective response rate was 61% for patients receiving the combination versus 11% for patients receiving ipilimumab alone. Complete responses were seen in 22% of the combination arm with none in the ipilimumab arm and responses were seen regardless of *BRAF* mutational status. Median progression-free survival was significantly longer in the combination arm. As with previous studies, the responses were durable, with 82% of responding patients in the combination arm maintaining their response.[47]

One of the most significant concerns with a combination of two immune checkpoint inhibitors is the safety profile. In Checkmate-067, grade 3 or 4 treatment-related adverse drug reactions were significantly higher with the combination arm than nivolumab or ipilimumab alone.[45] Similar safety results were observed in Checkmate-069, with grade 3 or 4 drug-related adverse reactions occurring more frequently in the combination arm than ipilimumab alone.[47] As a result of the data from these two trials, the FDA granted approval for combination therapy with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for four doses followed by nivolumab maintenance (240 mg every 2 weeks or 480 mg every 4 weeks) in patients with unresectable or metastatic melanoma. While this combination offers higher response rates with the potential for durable responses, judicious monitoring and aggressive management of toxicities are important.

Summary of Immune Checkpoint Inhibitors

Over the last decade, advances in immunotherapy have provided new treatment options and offered new hope regarding survival for patients with metastatic melanoma. These benefits are realized with single-agent or combination immune checkpoint inhibitors. Despite advances in the treatment of melanoma, several questions still surround the use of immunotherapy. First, how do we identify which patients will benefit from immunotherapy treatment? Some clinicians are hesitant to treat older patients or those with autoimmune conditions with ipilimumab because of toxicity concerns. These unique patient populations require further investigation. Second, what are the biomarkers of response to immunotherapy? Immunologic markers and other biomarkers have been investigated without success.[48] Tumors that express PD-L1, regardless of the type of cancer, have demonstrated higher responses to PD-1/PD-L1 blockade. However, patients with tumors that do not express PD-1/PD-L1 may also benefit and should not be excluded from this treatment option. In addition, it remains unclear as to the best approach for assessing PD-L1 expression, definition of positivity in the assay, and clinical application.[40] Lastly, what is the optimal sequencing of systemic therapy with immunotherapy and targeted therapy? A recent study (DREAMseq) evaluated the sequencing of initial treatment with combination immunotherapy versus combination targeted therapy. Patients with untreated *BRAF* V600-mutant metastatic melanoma were randomized to receive initial therapy with nivolumab and ipilimumab or dabrafenib and trametinib; patients were crossed over to the alternate combination at progression. Initial overall response rates were similar at 46% with nivolumab and ipilimumab versus 43% with dabrafenib and trametinib. However, 88% of patients who responded to nivolumab and ipilimumab remained in response compared to 49% of those who responded to dabrafenib and trametinib. In addition, response rates to nivolumab and ipilimumab were lower in the second-line setting, which suggests that combination immunotherapy is less effective after progression on dabrafenib and trametinib. A meaningful difference in overall survival was observed. At a median follow-up of 27.7 months, overall survival for the nivolumab and ipilimumab group was 72% compared to 52% for dabrafenib and trametinib, a 20% absolute difference in survival.[49] These results suggest that the combination of nivolumab and ipilimumab is preferred as initial therapy over BRAF and MEK inhibitor combination therapy.

Other Immunotherapy Approaches

Vaccine therapy has been investigated for over a decade in metastatic melanoma. The rationale for vaccination is that antigens expressed on the surface of tumor cells differ from normal cells and a vaccine has the ability to induce effective tumor-specific immune responses with less toxicity than conventional chemotherapy or other immunotherapies.

A variety of melanoma vaccines, based on whole tumor cells, peptides, and proteins have been evaluated to treat patients with metastatic disease or intermediate-risk and high-risk patients following surgical resection. To date, no vaccine has shown a survival advantage.[11] Occasional clinical responses have been observed in trials of melanoma vaccines. Vaccines in combination with other biologic therapies have been evaluated. Although early efficacy signals have been seen with some combination approaches, none have improved survival.[11] Clinical trials that incorporate vaccines into approved immunotherapeutic treatments are ongoing.

Oncolytic immunotherapy has been investigated for the treatment of metastatic melanoma. Talimogene laherparepvec (T-VEC) is a genetically modified oncolytic virus derived from herpes simplex-1. T-VEC works by two distinct mechanisms: (1) modification of attenuated HSV-1 to selectively replicate within tumor cells causing death while sparing other cells and (2) secretion of GM-CSF to attract dendritic cells to the site for antigen presentation and T-cell activation. Activated T cells can then target the cancer cells systemically. In a phase III study, T-VEC demonstrated better response rates (including complete responses) and a trend toward improved survival compared to GM-CSF alone.[50] It was well tolerated with fatigue, chills, and fever being the most common adverse drug reactions with few severe events reported. T-VEC is FDA-approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with recurrent melanoma after initial surgery. T-VEC is administered intratumorally (injected directly into the tumor) and therefore patients with internal visceral disease are not appropriate candidates for treatment. With its favorable toxicity profile, T-VEC has been studied in combination with other immunotherapies. Masterkey-265 was a phase III, randomized, double-blind study evaluating the use of TVEC plus pembrolizumab versus pembrolizumab alone in unresectable or metastatic melanoma. Unfortunately, the combination did not significantly improve progression-free or overall survival, indicating that TVEC did not add any additional benefit to PD-1 inhibitor monotherapy.[51]

Targeted Therapy

Oral kinase inhibitors have emerged as standard therapy for malignancies such as renal cell carcinoma, chronic myelogenous leukemia, subsets of lung cancer, and gastrointestinal stromal tumors. As our understanding of the biology of melanoma grows, there is increasing interest in developing therapies against molecular targets involved in the development and progression of melanoma. Several orally administered targeted therapies are FDA-approved to treat melanoma (see Tables 162-7 and 162-8).

TABLE 162-7

Dosing of BRAF Inhibitors in Melanoma

Drug	Brand Name	Dose	Dose Reductions for Adverse Drug Reactions	Food-Drug Interaction	Drug-Drug Interactions
Dabrafenib	Tafinlar	• 150 mg BID • Missed dose may be taken up to 6 hours prior to next dose	• First: 100 mg BID • Second: 75 mg BID • Third: 50 mg BID • Subsequent: permanently discontinue if unable to tolerate 50 mg BID	• Take at least 1 hour before or 2 hours after a meal • High-fat meals decrease C_{max} and AUC	• Dabrafenib may decrease drug levels of CYP2B6, CYP2C19, CYP2C8, CYP2C9, and CYP3A4 substrates • Strong CYP2C8 and CYP3A4 inhibitors may increase dabrafenib concentrations • Concurrent use with antacids, H2-antagonists, and proton pump inhibitors may decrease dabrafenib concentrations • Concurrent use with St. John's wort may decrease dabrafenib concentrations • Monitor closely if dabrafenib is used concurrently with other drugs known to prolong QT interval

Encorafenib	Braftovi	• 450 mg daily • Missed dose may be taken up to 12 hours prior to next dose	• First: 300 mg daily • Second: 200 mg daily • Subsequent: permanently discontinue if unable to tolerate 200 mg daily	• Take with or without food • Avoid grapefruit juice	• Strong and moderate CYP3A4 inhibitors may increase encorafenib concentrations • Reduce encorafenib dose to one-third original dose if used concurrently with strong CYP3A4 inhibitor • Reduce encorafenib dose to one-half original dose is used concurrently with moderate CYP3A4 inhibitor • Strong or moderate CYP3A4 inducers may decrease encorafenib concentrations • Encorafenib may increase toxicity or decrease efficacy of sensitive CYP3A4 substrates • Coadministration with hormonal contraceptives can result in decreased concentrations and loss of efficacy • Avoid coadministration of encorafenib with other drugs known to prolong QTc interval
Vemurafenib	Zelboraf	• 960 mg BID • Missed dose may be taken up to 4 hours prior to next dose	• First: 720 mg BID • Second: 480 mg BID • Subsequent: permanently discontinue if unable to tolerate 480 mg BID	• Take with or without food • Avoid grapefruit juice	• Avoid concomitant administration with CYP1A2 substrates with a narrow therapeutic window • Strong CYP3A4 inhibitors/inducers may increase/decrease vemurafenib concentrations and should be avoided • Vemurafenib may increase concentrations of CYP2D6 substrates • Avoid concurrent use with P-gp substrates known to have narrow therapeutic indices • Monitor closely if vemurafenib is used concurrently with other drugs known to prolong QT interval

AUC, area under the curve; CYP, cytochrome P450.

TABLE 162-8

Dosing of MEK Inhibitors in Melanoma

Drug	Brand Name	Dose	Dose Reductions for Adverse Drug Reactions	Food-Drug Interactions	Drug-Drug Interactions
Binimetinib	Mektovi	• 45 mg BID • Missed dose may be taken up to 6 hours prior to the next dose	• First: 30 mg BID • Subsequent: permanently discontinue if unable to tolerate 30 mg BID	• Take with or without food	• No known significant interactions
Cobimetinib	Cotellic	• 60 mg daily on days 1-21 of 28-day cycle	• First: 40 mg daily • Second: 20 mg daily • Subsequent: permanently discontinue if unable to tolerate 20 mg daily	• Take with or without food	• CYP3A4 inducers may decrease cobimetenib concentrations • CYP3A4 inhibitors may increase cobimetenib concentrations
Trametinib	Mekinist	• 2 mg daily • Store in the refrigerator (36-46°F [2-8°C]) • Missed dose may be taken up to 12 hours prior to the next dose	• First: 1.5 mg daily • Second: 1 mg daily • Permanently discontinue if unable to tolerate 1 mg daily	• Take at least 1 hour before or 2 hours after a meal • High-fat meals may decrease AUC	• May enhance the adverse effects of dabrafenib

AUC, area under the curve; CYP, cytochrome P450.

Vemurafenib was the first BRAF inhibitor developed to treat patients with metastatic melanoma who harbor a V600E mutation. In a phase III trial comparing vemurafenib with dacarbazine in patients with unresectable, previously untreated stage IIIC or IV melanoma with a *BRAF* V600E mutation, vemurafenib significantly improved response rate and overall survival. Patients treated with vemurafenib had longer median progression-free survival and a higher overall survival rate at 6 months. The median time-to-response was also shorter with vemurafenib than dacarbazine.[8]

Dabrafenib, another oral selective BRAF inhibitor, demonstrated similar activity to vemurafenib in early-stage clinical trials in patients with previously untreated *BRAF* V6000E mutated melanoma. In a phase III study, dabrafenib was compared to dacarbazine in patients with untreated stage IV or unresectable stage III melanoma. Patients in the dabrafenib arm had longer median progression-free survival. A follow-up analysis showed that overall survival at 12 months was 70% with dabrafenib as compared to 63% with dacarbazine.[8] Both vemurafenib and dabrafenib have been studied in melanoma patients with CNS metastasis with some activity. Other targeted agents, such as the pan-RAF inhibitor sorafenib, have historically been studied in this setting without encouraging results.[8]

BRAF inhibitors are generally well tolerated (see Table 162-9). Skin complications, comprising of cutaneous squamous cell carcinoma or keratoacanthoma and photosensitivity reactions, are a major concern with the use of these agents. In clinical trials, the incidence of cutaneous squamous cell carcinoma or keratoacanthoma with vemurafenib was 18% and 6% with dabrafenib. The development of these lesions result from the activation of the MAPK pathway in healthy skin cells lacking *BRAF* alterations. As a result, patients receiving a BRAF inhibitor should have dermatologic evaluations prior to starting therapy, every 2 months while on therapy and for up to 6 months following discontinuation of therapy. Cutaneous complications can be effectively managed by surgical resection and treatment with the BRAF inhibitor can continue without dose adjustment.[52]

TABLE 162-9

Monitoring of BRAF Inhibitors in Melanoma

Drug	Adverse Drug Reactions		Monitoring Parameters	Comments
	Common	Rare but Serious		
Dabrafenib	• Pyrexia • Rash • Chills • Headache • Arthralgia • Fatigue • Hyperkeratosis • Nausea/vomiting/diarrhea • Alopecia • Palmar-plantar erythrodysesthesia • Increased LFTs • Hyperglycemia • Hypophosphatemia	• New primary malignancies (cutaneous and noncutaneous) • Hemorrhage • Uveitis • Pancreatitis • Interstitial nephritis	• CMP including serum phosphorus, albumin, glucose, and LFTs • CBC for myelosuppression • Dermatologic examinations at baseline, every 2 months during treatment, then 6 months after discontinuation for secondary skin malignancies • ECG for QT prolongation • Signs/symptoms of uveitis (vision changes, photophobia, eye pain)	• Risk of secondary skin malignancies decreases when used in combination with MEK inhibitor • ECHO to assess LVEF when used in combination with MEK inhibitor • Patients with G6PD deficiency are at risk for hemolytic anemia
Encorafenib	• Fatigue • Nausea/vomiting • Abdominal pain • Arthralgia • Rash • Myopathy • Hyperkeratosis • Headache • Anemia • Increased LFTs • Pyrexia	• New primary malignancies (cutaneous and noncutaneous) • Hemorrhage • Uveitis • QTc prolongation	• Dermatologic evaluation prior to, while on therapy, and following discontinuation of treatment • CMP including serum phosphorus, magnesium, glucose, and LFTs • ECG for QT prolongation; electrolytes before and during treatment • Signs/symptoms of uveitis (vision changes, photophobia, eye pain)	• Only FDA-approved in combination with binimetinib • If binimetinib is held, the encorafenib dose must be reduced to 300 mg daily
Vemurafenib	• Arthralgia • Rash • Alopecia • Fatigue • Nausea • Photosensitivity • Pruritus • Skin papilloma	• New primary malignancies (cutaneous and noncutaneous) • Uveitis • QTc prolongation • Severe dermatologic reactions (SJS, TEN) • Hypersensitivity reactions (including DRESS)	• LFTs at baseline and monthly or as clinically indicated • Serum creatinine at baseline and periodically during treatment • ECG and electrolytes (including potassium, magnesium, and calcium) at baseline, after 15 days, monthly for the first 3 months, then every 3 months or as clinically indicated • Dermatologic examinations at baseline, every 2 months during treatment. Consider monitoring for 6 months following discontinuation • Signs/symptoms of uveitis (vision changes, photophobia, eye pain)	• Off-label indication for *BRAF* V600K mutation • Associated with rare cases of pancreatitis; evaluate unexplained abdominal pain • Due to photosensitivity, patients should avoid the sun, wear protective clothing, and wear sunscreen

		• Renal failure	• Monitor closely if administered concomitantly or sequentially with radiation treatment	

CMP, comprehensive metabolic panel; CBC, complete blood count; CPK, creatine phosphokinase; DVT, deep vein thrombosis; DRESS, drug reaction with eosinophilia and systemic symptoms; LFTs, liver function tests; LVEF, left ventricular function; PE, pulmonary embolism.

Resistance to BRAF inhibitors is potentially caused by mutations in *MEK*, dependency on MEK/ERK antiapoptotic signaling, PI3K/AKT pathway involvement, *NRAS* mutation, or MAPK pathway reactivation. Concurrent treatment with an MEK inhibitor in combination with a BRAF inhibitor can delay the onset of acquired resistance.

MEK inhibitors have been studied in the treatment of metastatic melanoma and have shown modest activity as monotherapy. Trametinib is an oral small-molecule inhibitor of MEK1/2 that was studied in a phase III trial that compared trametinib to chemotherapy (dacarbazine or paclitaxel). In this trial, median progression-free survival was 4.8 versus 1.5 months in the trametinib and chemotherapy arms, respectively. Overall survival at 6 months was 81% for trametinib and 67% for chemotherapy, even with crossover at progression. Common adverse drug reactions seen with trametinib were rash, diarrhea, and peripheral edema (see Table 162-10). Interestingly, secondary skin neoplasms were not observed in this trial.[8]

TABLE 162-10

Monitoring of MEK Inhibitors in Melanoma

Drug	Adverse Drug Reactions		Monitoring Parameters	Comments
	Common	Rare but Serious		
Binimetinib	• Fatigue • Nausea/vomiting • Abdominal pain • Diarrhea • Constipation • Rash • Increased LFTs • Anemia • Increased creatinine • Increased CPK • Hyponatremia	• VTE • Cardiomyopathy • Ocular toxicity (serous retinopathy/retinal pigment epithelial detachments, retinal vein occlusion) • Interstitial lung disease/pneumonitis • New primary malignancies (cutaneous and noncutaneous) • Hemorrhage • Rhabdomyolysis	• LFTs at baseline, monthly during treatment, and as clinically indicated • CPK and serum creatinine at baseline, periodically during treatment, and as clinically indicated • Assess for visual symptoms at each visit. Perform ophthalmologic examination at regular intervals and for any new/worsening visual disturbances • Signs and symptoms of bleeding • LVEF at baseline, 1 month after therapy initiation, then at 2- to 3-month intervals for cardiomyopathy • Evaluate for signs/symptoms of pulmonary toxicity (cough, dyspnea, hypoxia, pleural effusions, infiltrates)	• If encorafenib is permanently discontinued, discontinue binimetinib • Serous retinopathy occurred in 20% of patients treated with binimetinib in combination with encorafenib • Elevation in LFTs can occur with combination; monitor prior to beginning treatment and monthly during treatment
Cobimetinib	• Nausea/vomiting • Diarrhea	• Cardiomyopathy • Hemorrhage	• CMP at baseline and monthly during treatment for	• Due to photosensitivity, patients should avoid the

	• Hypertension • Photosensitivity • Pyrexia • Hypophosphatemia • Electrolyte disturbances • Hypoalbuminemia • Lymphopenia • Anemia • Increased LFTs • Increased CPK • Increase in serum creatinine • Hyponatremia	• New primary malignancies (cutaneous and noncutaneous) • Ocular toxicity (serous retinopathy, retinal vein occlusion • Hepatotoxicity • Rhabdomyolysis	hepatotoxicity, renal failure, and electrolyte replacement • CPK at baseline, periodically during treatment, and as clinically indicated • LVEF at baseline, 1 month after initiation of therapy, and every 3 months until discontinuation • Dermatologic examinations at baseline, every 2 months during treatment, then 6 months after discontinuation for secondary skin malignancies • Ophthalmological evaluation at regular intervals and at any sign of new or worsening visual disturbances • Signs and symptoms of hemorrhage and rhabdomyolysis	sun, wear protective clothing, and wear sunscreen • Hypertension has been seen in combination with vemurafenib
Trametinib	• Dermatologic toxicity (rash, acneiform dermatitis, palmar-plantar erythrodysesthesia, erythema) • Diarrhea • Lymphedema (including edema, peripheral edema) • Pyrexia • Hypertension • Fatigue • Nausea/vomiting • Hyperglycemia • Increased LFTs • Anemia • Hypoalbuminemia	• VTE • Cardiomyopathy • Ocular toxicity (retinal pigment epithelial detachments, retinal vein occlusion) • Interstitial lung disease/pneumonitis • New primary malignancies (cutaneous and noncutaneous) • Hemorrhage • Colitis/GI perforation • Rhabdomyolysis	• CBC and CMP at baseline and as clinically indicated • LVEF at baseline, 1 month after therapy initiation, then at 2- to 3-month intervals • Ophthalmological evaluation periodically and at any sign of visual disturbance • Evaluate for signs/symptoms of pulmonary toxicity (cough, dyspnea, hypoxia, pleural effusions, infiltrates) • Blood pressure • Signs and symptoms of bleeding • Dermatologic examinations at baseline, every 2 months during treatment, then 6 months after discontinuation • Monitor closely for colitis and GI perforation	• Severe skin toxicities can require hospitalization • Intracranial hemorrhage can be fatal • Many adverse effects are increased when trametinib is used in combination with dabrafenib • Increased incidence of DVT/PE when used in combination with dabrafenib • Increase in serious febrile reactions when used in combination with dabrafenib

CMP, comprehensive metabolic panel; CBC, complete blood count; CPK, creatine phosphokinase; DVT, deep vein thrombosis; DRESS, drug reaction with eosinophilia and systemic symptoms; LFT's, liver function tests; LVEF, left ventricular function; PE, pulmonary embolism; VTE, venous thromboembolism.

In addition to delaying drug resistance, the combination of BRAF and MEK inhibitors shows additive efficacy in the treatment of melanoma. The combination of trametinib 2 mg orally once daily and dabrafenib 150 mg orally twice daily received accelerated approval for treatment in patients with unresectable or metastatic melanoma with *BRAF* V600 mutations based on higher objective response rates compared to either agent alone. Additional trials with this combination compared to BRAF inhibitors in the same patient population confirmed early findings and led to a full FDA approval. In a

clinical trial that compared the combination to dabrafenib alone, patients randomized to the combination had longer median progression-free survival, overall survival at 6 months and higher overall response rates as compared with dabrafenib alone.[53] In another phase III trial, the combination of dabrafenib and trametinib showed significantly longer median overall survival and higher overall survival at 12 months. Median progression-free survival was also significantly longer and the overall response rate was higher in patients treated with the combination.[54] The safety profile with the combination was similar to that observed with either drug given alone, with the notable exception of decreased incidence of skin complications in the combination arms.

Cobimetinib is another inhibitor of MEK1/2 approved in combination with vemurafenib to treat patients with unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation. The recommended dosing with this regimen is vemurafenib 960 mg orally twice daily on days 1 to 28 and cobimetinib 60 mg orally once daily on days 1 to 21 of a 28-day cycle. In a phase III trial, median progression-free survival was significantly improved with the combined regimen of cobimetinib and vemurafenib versus vemurafenib alone. The difference in median overall survival was also statistically significant in favor of the combination. Overall response rates were 70% and 50% for the combination and single-agent arms, respectively. Adverse drug reactions were similar across the two groups and similar to the other MEK and BRAF combination, the number of secondary cutaneous cancer was decreased.[55]

The safety and efficacy of encorafenib and binimetinib, a BRAF and MEK inhibitor combination, were established in the COLUMBUS trial, a phase III study where 577 patients were randomized to receive encorafenib 450 mg daily plus binimetinib 45 mg twice daily, encorafenib 300 mg daily, or vemurafenib 960 mg twice daily. Median progression-free survival was significantly longer with the combination as compared with vemurafenib alone. The overall response rate was higher with encorafenib and binimetinib as compared to BRAF inhibitor monotherapy. The median overall survival was 33.6 months for the combination of encorafenib and binimetinib as compared to 16.9 months with vemurafenib. This is the longest overall survival observed of all studies conducted with combination BRAF and MEK inhibitors. The adverse drug reactions seen with encorafenib and binimetinib are similar to those of other BRAF and MEK inhibitor combinations.[56]

Another agent of interest in the treatment of metastatic melanoma is imatinib mesylate, an oral agent that inhibits *KIT* and platelet-derived growth factor receptor. *KIT* is expressed primarily in acral and mucosal melanomas and treatment with imatinib showed activity against melanoma cell growth in preclinical studies. In clinical trials with unselected patients, imatinib did not show benefit in metastatic melanoma despite downregulation of phosphorylated *KIT*.[8] However, a phase II trial of imatinib in patients with *KIT* mutations reported that 23% had a partial response, 30% had stable disease, and progression-free survival was 3.5 months.[8] Responses in these patients were short, similar to what is seen with BRAF inhibitor monotherapy. Other potential molecular targets in the treatment of melanoma include vascular endothelial growth factor and cyclin-dependent kinases. Studies with drugs that inhibit these pathways are ongoing.

Combination Targeted Therapy Plus Immunotherapy

With the success of both immunotherapy and targeted therapy, combining agents from both classes is another area of great interest and ongoing research interest. Studies combining ipilimumab with BRAF inhibitors have been conducted but are associated with significant toxicity. A phase I trial combining vemurafenib and ipilimumab showed high rates of hepatotoxicity while case reports of dabrafenib/trametinib plus ipilimumab resulted in severe gastrointestinal toxicity, specifically perforation. Based on these results, the use of targeted therapy in combination with ipilimumab is not recommended.[8]

The combination of BRAF and MEK inhibitors plus other immune checkpoint inhibitors has shown promising results in the treatment of metastatic melanoma. IMspire150, a Phase III, double-blind study, randomized 514 patients with untreated *BRAF* V600-mutated metastatic melanoma to receive combination BRAF and MEK inhibitors (vemurafenib and cobimetinib) and either atezolizumab or placebo. At a median follow-up of 18.9 months, the median progression-free survival was significantly longer in patients treated with combination BRAF and MEK inhibitors and atezolizumab versus combination BRAF and MEK inhibitors alone (15.1 vs 10.6 months). Common treatment-related adverse drug reactions that occurred more frequently in the atezolizumab arm were increased blood creatinine phosphokinase, pyrexia, arthralgia, myalgia, increased liver enzymes and bilirubin, hyper/hypothyroidism, pneumonitis, pruritus, and peripheral edema.[57] Based on this study, the combination of vemurafenib, cobimetinib, and atezolizumab was FDA-approved for the treatment of patients with *BRAF* V600 mutation-positive unresectable or metastatic melanoma and is also recommended per the NCCN guidelines in this treatment setting.[8] The dosing for this regimen includes a run-in period with vemurafenib 960 mg by mouth twice daily for 21 days then 720 mg twice daily thereafter plus cobimetinib 60 mg daily days 1 to 21 every 28 days in addition to atezolizumab 840

mg IV every 2 weeks. Another BRAF and MEK inhibitor combination (dabrafenib and trametinib) has also been studied in combination with immunotherapy. Keynote-022 was a double-blind, phase II study evaluating the use of dabrafenib and trametinib and either pembrolizumab or placebo for patients with untreated *BRAF* V600-mutated advanced melanoma. This study showed that at 36.6 months of follow-up, the addition of immunotherapy to combination BRAF and MEK inhibitor therapy substantially improved progression-free survival, duration of response, and overall survival but with a higher incidence of treatment-related adverse drug reactions. These results show the importance of careful patient selection to identify the best candidates for combined modality therapy.[58]

Radiation

The role of radiation in the adjuvant treatment of melanoma has been investigated. Recent data from a prospective study suggest patients treated with therapeutic lymphadenectomy for lymph node relapse benefit from postoperative radiation to the nodal basins as compared to observation. Lymph node recurrence was significantly less in the adjuvant radiation arm, but increased toxicity was noted. No difference in overall survival or relapse-free survival was observed between the groups.[59] Adjuvant radiation may be an acceptable option for selected patients. Radiation can also be used in patients with in-transit metastasis, satellite metastasis, or for extranodal tumor extension. For patients with metastatic melanoma, radiation is palliative to symptomatic areas of disease progression. Stereotactic radiosurgery (SRS), or stereotactic radiotherapy (SRT), is the preferred type of treatment for brain metastases. Adjuvant radiation, given after resection of brain metastases, can help with disease control. Whole brain radiation is associated with worse cognitive decline compared to SRS/SRT, and therefore should be used in situations when SRS/SRT is not achievable.[60] Whole brain radiation may be needed in situations that involve numerous brain metastasis or leptomeningeal disease.

Limb Perfusion and Limb Infusion

Isolated limb perfusion is a surgical procedure involving regional intravascular delivery of chemotherapy or biotherapy (or both) into an extremity with cutaneous melanoma. When in-transit metastases occurs in extremities, local therapy with isolated limb perfusion or isolated limb infusion has been used.[8] Isolated limb perfusion is a method for escalating the dose of chemotherapeutic drugs to a specific region of the body while limiting the systemic toxicities of the agent. Most perfusions can be performed with drug exposures of less than 2%. The most significant adverse drug reaction of isolated limb perfusion is regional toxicity because the skin, subcutaneous tissue, and tissue of the extremity receives the same dose and is subjected to the same perfusion conditions as the tumor located within the extremity. After regional perfusions, objective response rates greater than 50% in treated limbs have been reported, with overall response rates possibly as high as 80%. Although most clinical trials have used melphalan, it is not known whether the combination of melphalan with other agents may improve results.[8] This is also a technically complex procedure that should only be performed at centers with the proper clinical expertise. A simplified form of isolated limb perfusion, called isolated limb infusion, is a low-flow isolated limb perfusion performed under hypoxic conditions via small-caliber arterial and venous catheters. It has been proposed that the hypoxia which develops during isolated limb infusion may be beneficial with certain cytotoxic agents such as melphalan.[8]

EVALUATION OF THERAPEUTIC OUTCOMES

The outcome of patients treated with melanoma depends on the stage of disease at presentation. The prognosis of patients with thin tumors (less than 1 mm in thickness) and localized disease is good with long-term survival in more than 90% of patients. The risk of regional nodal involvement rises with increasing tumor thickness and survival rates decrease in patients with nodal involvement. Long-term survival in patients with distant metastasis is even lower. Therefore, early diagnosis and appropriate treatment of early disease are essential. Patients with suspicious pigmented lesions should be evaluated and the lesion excised whenever possible. Treatment is determined by patient factors and stage of disease.

Clinical practice guidelines published by the NCCN and European Society of Clinical Oncology (ESMO) provide guidance for treatment and follow-up of patients with melanoma.[8,61] Intensive surveillance has the benefit of early detection of recurrent disease, which may lead to better options for surgical resection. Emphasis on the evaluation of locoregional areas is important. For patients with in situ melanoma, periodic skin examinations for life are recommended, with frequency determined based on patient risk factors. Local recurrence is associated with aggressive tumor biology and frequently is a manifestation of an aggressive primary tumor. If a local recurrence occurs after inadequate primary disease management, the patient should undergo a workup based on the lesion thickness of the original melanoma. Patients with nodal recurrence should be evaluated for lymph node metastasis. Patients with systemic recurrence should be evaluated and treated similarly to patients presenting with systemic disease.

CONCLUSION

Treatment of cutaneous melanoma is determined by both disease-related and patient-related issues. Treatment recommendations are based on stage of disease. Treatment of localized disease is surgical excision, with the extent of excision based on the tumor size. Wide excision is recommended for in situ melanoma and wide excision with SLNB for stage IA, IB, and II disease.

The addition of new immunotherapy and targeted agents has increased the number of adjuvant treatment options for patients with melanoma who are at high risk of recurrence. Identifying which patients are appropriate candidates for treatment after resection of the primary tumor remains a challenge. When choosing an adjuvant treatment, the clinician should consider patient preference, age, comorbidities, and risk of recurrence.[8]

Due to the rapid influx of effective therapies, the management of metastatic melanoma has become complex. The NCCN guidelines list a variety of preferred systemic therapies for advanced or metastatic melanoma, including ipilimumab/nivolumab, pembrolizumab, nivolumab, combination BRAF and MEK inhibitors, triple therapy with BRAF and MEK inhibitors plus PD-1 (or PD-L1) inhibitor, ipilimumab, high-dose aldesleukin, and in certain cases chemotherapy or other targeted agents.[8] The choice of drug therapy should be based on *BRAF* mutational status, the aggressiveness of the disease, and disease-related symptoms. Patients with a more indolent clinical picture may respond better to immunotherapy. Patients with a documented *BRAF* mutation are candidates for treatment with a BRAF and MEK inhibitor combination regimen. Best supportive care is also an option for some individuals. Surgical treatment of metastatic melanoma should be considered in select individuals based on the extent and location of disease and performance status.

ABBREVIATIONS

AJCC	American Joint Committee on Cancer
ALM	acral lentiginous melanoma
ARF	alternative reading frame
CSD	chronic sun damage
CTL	cytotoxic T lymphocyte
CTLA-4	cytotoxic T lymphocyte antigen 4
ECOG	Eastern Cooperative Oncology Group
EORTC	The European Organization for Research and Treatment of Cancer
ESMO	European Society of Clinical Oncology
FAMMM	familial atypical multiple mole syndrome
FDA	Food and Drug Administration
HLA	human leukocyte antigen
IL-2	interleukin-2
irAE	immune-related adverse effect
JAK	janus-kinase

LAK	lymphokine-activated killer
LDH	lactate dehydrogenase
LMM	lentigo maligna melanoma
MAPK	mitogen-activated protein kinase pathway
mTOR	mammalian target of rapamycin
NCCN	National Comprehensive Cancer Network
NK	natural killer
NMSC	nonmelanoma skin cancer
NSAID	nonsteroidal anti-inflammatory drug
PD-1	programmed death receptor 1
PD-L1	programmed death receptor 1 ligand
PET	positron emission tomography
PI3K	phosphatidylinositol-3 kinase
SLNB	sentinel lymph node biopsy
SPF	sun protection factor
SRS	stereotactic radiosurgery
SRT	stereotactic radiotherapy
SSE	skin self-examination
SSM	superficial spreading melanoma
STAT	signal-transducer-and-activator-of-transcription
TNF	tumor necrosis factor
TIL	tumor-infiltrating lymphocyte
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
VEGF	vascular endothelial growth factor

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