HOSPITAL PHYSICIAN®

ONCOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

NOTE FROM THE PUBLISHER:
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Cutaneous Melanoma

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INTRODUCTION

Melanoma is the sixth most common cancer in the United States and the leading cause of deaths among all cutaneous malignancies.[1,2] In 2012, it was estimated that approximately 75,000 individuals were diagnosed with melanoma and more than 9000 died. The incidence of melanoma is rising the fastest among all major malignancies,[3] and the lifetime risk of melanoma among men and women now exceeds 1 in 68, as compared with 1:1500 in 1930.[4] The incidence of melanoma is predicted to continue increasing, and there has been no corresponding decrease in mortality.[3] This case-based review summarizes the etiology, risk factors, clinical presentation, and management of cutaneous melanomas, which comprise the majority of melanoma cases. The biology and management for other noncutaneous melanomas (such as mucosal or ocular melanomas) are beyond the scope of this review.

ETIOLOGY AND RISK FACTORS

Melanoma has been proposed to arise through a stepwise progression of molecular lesions in a melanocyte.[5] Nevi arising from proliferating melanocytes acquire sequential genetic lesions that lead to dysplasia, invasion, and ultimately metastasis. This process is influenced by both environmental and genetic factors. Although it has not been possible to prove experimentally, exposure to ultraviolet light (sunlight) has been strongly implicated as an important causative factor,[6] and ultraviolet signature mutations are commonly detected in the genomes of melanoma.[7] The incidence of melanoma correlates with geographic latitude, with higher incidence close to the equator and progressively lower incidence toward the poles.[8,9] Ultraviolet B (wavelengths 290–320 nm) is most closely associated with melanoma, although ultraviolet A wavelength exposure in tanning salons also correlates with melanoma risk.[10–12] The pattern of exposure to ultraviolet light also appears to be important, as intermittent, intense exposure in childhood carries more risk than chronic, low-level of exposure.[11]

Despite the association between ultraviolet light and melanoma, other intrinsic factors such as skin color can influence the risk in an ultraviolet-independent manner.[13] There are great variations in melanoma incidence among races,[14] with the

highest risk among patients with a tendency to burn rather than tan.[15,16] Pigmentation characteristics strongly influence melanoma risk, with the so-called "red-head" phenotype (ie, red hair and fair complexion) associated with the highest risk of melanoma. This phenotype results in part from a point mutation that alters the receptor for melanocyte-stimulating hormone,[17] which may account for the higher risk of melanoma in European populations.[18,19] Men also are 1.5 times more likely to develop melanoma than women.[2]

Many individuals with melanoma can recount a premalignant precursor mole lesion,[20–22] which also places an individual at higher risk.[23] Approximately 10% of patients with melanoma have at least 1 first-degree relative with melanoma, but the etiologic basis for this association is unclear in most cases.[24] Individuals with germ-line mutations in the CDK4 locus or the CDKN2A gene (which encodes the cell cycle inhibitor p16) have a significantly increased risk of melanoma.[25,26] Although genetic testing is available on a commercial basis, the presence of the mutation does not alter management and the benefit of carrier identification has not been demonstrated.[27] BRCA2 mutations have been associated with increased risk of melanoma,[28] and small nucleotide polymorphisms that are associated with melanoma risk have also been identified.[29,30]

CLINICAL EVALUATION AND INITIAL MANAGEMENT

CASE PRESENTATION

A 52-year-old Caucasian man presents to his primary care physician after his wife noticed that a mole on his back has grown over the past year. He has no significant family or medical history. A physical examination reveals a thin, otherwise well-appearing man with an Eastern Cooperative Oncology Group performance status of 1. On examination, there is an asymmetric brownish-black mole on his back that measures 5 mm × 18 mm. The patient reports that the mole is itchy. There are no palpable lymph nodes, and the remainder of the examination is unremarkable. The patient undergoes a full-thickness excisional surgical biopsy for work-up of his lesion.

- **What are the signs and symptoms of melanoma?**

Clinical Features

The ABCDE (asymmetry, border, color, diameter, enlargement) rule has been widely popularized as a tool for screening of suspicious skin lesions.[31,32] Lesions that are asymmetric with border irregularity should raise suspicion of melanoma. The color of malignant lesions can range from varying shades of brown and black, but a bluish or pinkish tinge also may be seen. Most melanomas are associated with an evolution of a preexisting skin lesion[32] but are not associated with itching or pain; however, these latter 2 symptoms should also raise suspicion.[33] Dissemination of melanoma is quite varied and may occur by direct extension or by lymphatic or hematologic spread. Therefore, a complete physical examination with emphasis on common sites of metastasis, including lungs and lymph nodes, gastrointestinal tract, and brain and bone, is indicated in patients with a suspicious lesion.

Screening for melanoma by self-examination or by dermatologists is controversial and not uniformly recommended. The Canadian Task Force on Preventative Health Care concluded that there were insufficient data to recommend routine screening, although the American Cancer Society recommends skin examination every 3 years for all peo-

ple between ages 20 and 40 years and annually after age 40 years.[34] Patients at high risk, such as those with strong family history or individuals with a first-degree relative affected by melanoma, may warrant active surveillance.

CASE CONTINUED

Pathologic evaluation reveals a 1.1-mm thick melanoma with no ulceration, Clark level III with high mitotic rate but no microscopic satellites. Margins are 0.4 cm.

- **What are the most important prognostic factors?**

The depth of invasion, called Breslow thickness, of the original lesion in millimeters from the top (granular layer) of the epidermis to the underlying dermis is the most important predictive pathologic characteristic associated with recurrence. Increased depth of invasion is associated with an increased risk of recurrence, lymph node involvement, and death.[35,36] Pathologic ulceration represents a biologically more aggressive form of the disease and is now incorporated into the staging system.[35] Increased Clark level (a measure of the level of histologic invasion), increased mitotic rate, and the presence of microscopic satellites are also associated with higher risk.[35] Mitotic rate $\geq$1 per mm^2 is associated with worse prognosis, especially melanomas $\leq$1.0 mm of thickness,[7] which was incorporated into the 2010 American Joint Committee on Cancer (AJCC) staging classification.[7] Melanomas involving the extremity are associated with a better prognosis. However, clinical or pathologic involvement of lymph nodes is a poor prognostic factor, regardless of thickness or level (*see* "Sentinel Lymph Node Biopsy and Axillary Node Dissection").

- **What further studies should be performed for patients diagnosed with melanoma?**

After diagnosis of melanoma, a history and physical examination with complete skin examination are recommended. In patients with invasive melanoma, physical examination should include a comprehensive lymph node examination. Clinical staging guides further evaluation (**Table 1**) and correlates with outcome (**Figure**). Asymptomatic patients with relatively low-risk disease (Stage 0–II) do not require routine imaging, except to evaluate specific signs or symptoms as screening scans have quite a low yield and false-positive results are common.[37] For stage III patients with clinically positive lymph nodes, most clinicians perform a chest radiograph and measure lactic acid dehydrogenase (LDH) levels. Presence of regional metastasis should be determined using either fine-needle aspiration (FNA) or surgical biopsy. Although routine computed tomography (CT) screening scans are of low specificity,[38–40] many clinicians perform these scans in the initial work-up as a baseline for future scans. If inguinal/femoral lymphadenopathy is observed, a pelvic CT scan is recommended because of the poor specificity of the clinical examination.[41] For patients presenting with stage IV distant metastatic disease, an evaluation for additional metastatic disease should be undertaken.[41] Either FNA or open biopsy along with imaging of the chest, abdomen, and pelvis is warranted. Given the high risk for metastasis to the brain in advanced melanoma, magnetic resonance imaging (MRI) or a CT scan with contrast for even minimal signs or symptoms of central nervous system involvement is suggested.[41] LDH is not a specific or sensitive marker of melanoma, but its prognostic value in stage IV melanoma has led to its incorporation in the staging system.[42–47]

Table 1. 2010 AJCC TNM Staging Classification for Cutaneous Melanoma

Definitions		
Primary Tumor (T)		
TX	Primary tumor cannot be assessed (eg, curretaged or severely regressed melanoma)	
T0	No evidence of primary tumor	
Tis	Melanoma in situ	
T1	Melanomas ≤1.0 mm in thickness	
T2	Melanomas 1.01–2.0 mm	
T3	Melanomas 2.01–4.0 mm	
T4	Melanomas >4.0 mm	
Note	a and b subcategories of T are assigned based on ulceration and number of mitoses per mm^2, as shown below:	
T Classification	**Thickness (mm)**	**Ulceration Status/Mitoses**
T1	≤1.0	a: w/o ulceration and mitosis <1/mm^2
		b: with ulceration or mitoses ≥1/mm^2
T2	1.01–2.0	a: w/o ulceration
		b: with ulceration
T3	2.01–4.0	a: w/o ulceration
		b: with ulceration
T4	>4.0	a: w/o ulceration
		b: with ulceration
Regional Lymph Nodes (N)		
NX	Patients in whom the regional lymph nodes cannot be assessed (eg, previously removed for another reason)	
N0	No regional metastases detected	
N1–3	Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (intransit or satellite metastases)	
Note	N1–3 and a–c subcategories assigned as shown below:	
N Classification	**No. of Metastatic Nodes**	**Nodal Metastatic Mass**
N1	1 node	a: micrometastasis[1]
		b: macrometastasis[2]
N2	2–3 nodes	a: micrometastasis[1]
		b: macrometastasis[2]
		c: intransit met(s)/satellite(s) *without* metastatic node(s)
N3	4 or more metastatic nodes, or matted nodes, or intransit met(s)/satellite(s) with metastatic node(s)	
Distant Metastasis (M)		
M0	No detectable evidence of distant metastases	
M1a	Metastases to skin, subcutaneous, or distant lymph nodes	
M1b	Metastases to lung	
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH	
Note	Serum LDH is incorporated into the M category as shown below:	
M Classification	**Site**	**Serum LDH**
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

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Table 1. 2010 AJCC TNM Staging Classification for Cutaneous Melanoma *(continued)*

Anatomic Stage/Prognostic Groups							
	Clinical Staging[3]				Pathologic Staging[4]		
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
Stage IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
Stage IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
Stage IIC	T4b	N0	M0	IIC	T4b	N0	M0
Stage III	Any T	≥N1	M0	IIIA	T1–4a	N1a	M0
					T1–4a	N2a	M0
				IIIB	T1–4b	N1a	M0
					T1–4b	N2a	M0
					T1–4a	N1b	M0
					T1–4a	N2b	M0
					T1–4a	N2c	M0
				IIIC	T1–4b	N1b	M0
					T1–4b	N2b	M0
					T1–4b	N2c	M0
					Any T	N3	M0
Stage IV	Any T	Any N	M1	IV	Any T	Any N	M1

[1]Micrometastases are diagnosed after sentinel lymph node biopsy and completion lymphadenectomy (if performed).

[2]Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

[3]Clinical staging includes microstaging of primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

[4]Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

AJCC = American Joint Committee on Cancer; LDH = lactate dehydrogenase.

Adapted with permission from Balch CM, Gershenwald JE, Soong SJ. Melanoma of the skin. In: Edge SE, Byrd DR, Carducci MA, eds. AJCC cancer staging manual. 7th ed. New York: Springer; 2009: 325–44.

- **What is the next appropriate step in evaluation and initial management?**

SURGERY

For patients with localized disease, surgical wide excision with adequate margins is the primary treatment. Although surgical margins may need to be modified for anatomic or cosmetic reasons, several randomized studies have defined the recommended margins (**Table 2**). In patients with stage IA disease, wide excision with 1.0-cm margins is adequate.[48,49] For melanomas between

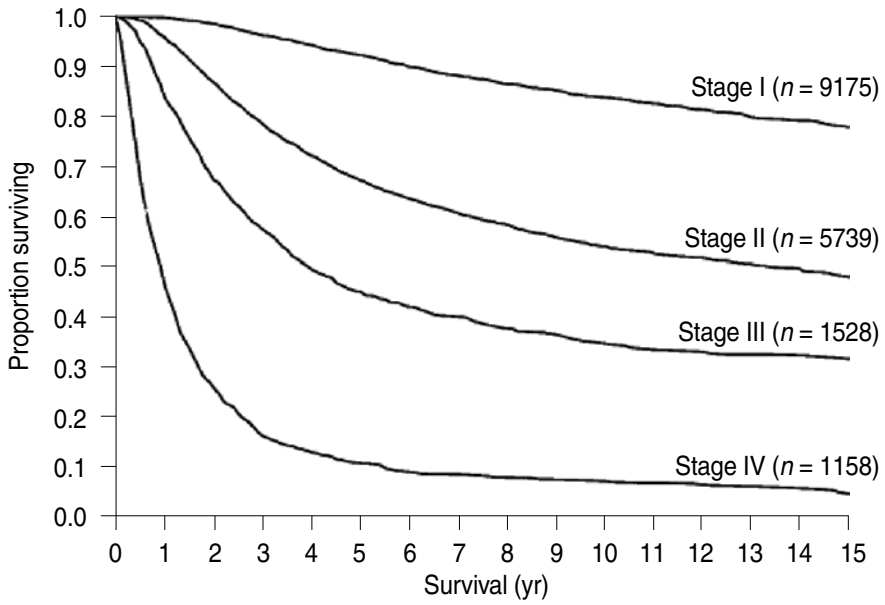

Figure. Fifteen-year survival for melanoma according to pathologic stage and location. (Adapted with permission from Balch CM, Buzaid AC, Soong SJ, et al. Final Version of the American Joint Committee on Cancer staging system for cutaneous melanoma. J Clin Oncol 2001;19:3637.)

1 and 2.0 mm in thickness, margins between 1 and 2 cm are recommended,[50] and 2.0-cm margins are indicated for thicker melanomas. Four-centimeter margins do not provide any improvement in local control of melanomas that are between 1.0 and 4.0 mm in thickness, whereas 3-cm margins provide a slightly lower rate of recurrence (but not survival) than 1-cm margins in melanomas that are 2 mm thick.[51]

Sentinel Lymph Node Biopsy and Axillary Node Dissection

Several studies have evaluated the utility of identifying and removing deposits of melanoma in lymph nodes.[52] Patients with early-stage melanoma limited to an extremity were randomized to immediate axillary node dissection or axillary node dissection at the time of regional metastasis. Although none of the studies showed benefit to immediate dissection, analysis showed that node dissection increased survival in patients with known regional node metastasis only.[52–54] These results suggested that axillary node dissection should be performed in patients with nodal disease and led to development of the sentinel node biopsy hypothesis.

The sentinel node biopsy hypothesis proposes that the primary draining lymph node predicts downstream involvement. This procedure identifies candidates for complete lymph node dissection and possible adjuvant therapy. However, in patients with intermediate thickness primary melanoma, sentinel lymph node biopsy (SLNB) followed by completion lymph node dissection, if appropriate, is not associated with improved melanoma-specific survival compared to those who were observed and delayed therapeutic lymphadenectomy, if necessary.[55] There is an improvement

Table 2. Surgical Margin Recommendations for Melanoma Excision

Tumor Thickness (mm)	Recommended Clinical Margins (cm)
In situ	0.5
≤1.0	1.0
1.01–2	1–2
2.01–4	2.0
>4	2.0

Data from Cascinelli,[48] Veronesi and Cascinelli,[49] Balch et al,[50] Thomas et al.[51]

in the 5-year disease-free survival with SLNB due to higher nodal relapse in the observation group. As a result, early lymph node dissection in patients with positive lymph nodes is the standard of care for intermediate thickness melanoma.[56,57] The importance of lymph node dissection in the setting of a positive sentinel lymph node is still unknown and is the subject of an ongoing randomized study, MSLT-2, in which patients with a positive sentinel lymph node are randomized to early lymph node dissection versus observation.[58,59]

TREATMENT

CASE CONTINUED

The patient undergoes a complete surgical resection and SLNB. He has 2.0-cm (adequate) margins and a positive sentinel lymph node. Completion lymph node dissection reveals a total of 3 lymph nodes with melanoma.

- **What are the treatment options for early-stage melanoma?**

ADJUVANT SYSTEMIC IMMUNOTHERAPY

For patients with node-negative melanoma with a high risk of recurrence (≤4.0-mm thick with ulceration, Clark level IV/V), adjuvant systemic immunotherapy should be considered. Low-dose interferon has been evaluated in multiple randomized trials for adjuvant treatment for melanoma. The French Cooperative Group Trial showed that adjuvant interferon therapy prolonged relapse-free survival with a trend towards increased overall survival.[60] In another study, low-dose interferon was associated with an improved disease-free survival.[61] In resected stage IIB and stage III patients, 2 studies (EORTC 18952 and AIM HIGH Study) compared adjuvant interferon with observation but showed no benefit in survival or progression-free survival.[62,63]

High-dose interferon alfa-2b for stage IIB/III resected melanoma has been studied in 3 randomized clinical trials. All 3 studies showed an improvement in relapse-free survival and 2 showed improved overall survival.[64–66] A larger follow-up study that included these studies[66] showed that benefit in relapse-free survival was maintained but not overall survival; a pooled analysis confirmed these results.[67] Compared with an experimental vaccine, high-dose interferon alfa-2b was associated with an improvement in relapse-free and overall survival.[66] Patients who had autoantibodies or signs of autoimmunity after treatment with high-dose interferon had improved overall and relapse-free survival.[68] More recently, patients with stage III melanoma who were randomly assigned to 5 years of subcutaneous pegylated interferon had significantly higher relapse-free survival but no difference in overall survival.[69] Subset analysis indicated that patients with N1 disease and an ulcerated primary did have a significant overall survival benefit, but prospective studies to confirm this observation are still underway.

Interferon is approved by the U.S. Food and Drug Administration for patients with lesions thicker

than 4 mm or melanoma involving lymph nodes as adjuvant therapy after successful surgery. Given the toxicity of high-dose interferon, the National Comprehensive Cancer Network (NCCN) failed to reach a consensus on the role of this adjuvant therapy.[41]

CASE CONTINUED

After a discussion of the adjuvant treatment options, the patient declines adjuvant therapy and chooses active surveillance.

- **What surveillance should be performed?**

Surveillance

For all patients diagnosed with melanoma, yearly skin examination is warranted, although this has not been rigorously evaluated. For local disease (stage IA), a complete physical examination with emphasis on regional nodes should be performed every 3 to 12 months,[70] but no specific radiologic investigations are recommended. For locoregional disease, NCCN guidelines suggest complete physical examinations every 3 to 6 months for 3 years, then every 4 to 12 months for 2 years and at least annually thereafter.[41] Chest radiograph, serum LDH, liver function tests, and complete blood count may be performed every 3 to 12 months apart but have very low yield.[71] CT scans, except to evaluate specific signs or symptoms, are not recommended.[41]

CASE CONTINUED

Two years after his diagnosis, the patient has been experiencing more fatigue than usual. Evaluation by his oncologist reveals anemia with hemoglobin of 7.9 g/dL. A CT scan shows multiple metastases in the abdomen. MRI of the brain does not reveal any abnormalities. A biopsy of a large liver lesion confirms melanoma. BRAF testing indicates the BRAF (V600E) mutation.

- **What are the treatment options for advanced-stage melanoma?**

The 5-year survival for patients with stage IV malignant melanoma is less than 20% (Figure).[41,72]

Surgery

For limited metastatic disease, resection may be indicated. Adjuvant systemic therapy following surgery has not been addressed by definitive clinical trials; therefore, a clinical trial should be considered. Options include single-agent chemotherapy, high-dose interleukin 2 (IL-2), combination chemotherapy, or clinical trials. In unresectable cases, these primary treatment options should also be considered (see below for details). Symptoms should prompt consideration of surgery or radiation for palliation. Brain metastases should prompt consideration of surgery or radiotherapy.[41]

Chemotherapy

Chemotherapy has limited effectiveness in metastatic melanoma. Dacarbazine (DTIC), the only approved single-agent chemotherapeutic agent, shows a 12% to 25% response rate, with a 4% to 5% complete response rate.[73] There has not been a phase III clinical trial to support any benefit to overall survival for any chemotherapy. Temozolomide, an analog of dacarbazine that is orally bioavailable, shows similar objective response rates to dacarbazine but has not been shown to be significantly better in objective measures or quality of life.[74] Nitrosoureas and platinum-based drugs have a response rate similar to dacarbazine. Many combination therapies utilizing the most active single agents may have higher response rates

than single agents but are more toxic and have not been associated with improved survival.[75]

Targeted Therapy

More recently, novel approaches exploiting the genetic perturbations of melanoma cells have led to therapies that target key molecular dependencies. Activating mutations of BRAF in melanoma[76] led to evaluation of the BRAF-selective drug vemurafenib in several trials.[77,78] In a phase III randomized clinical trial comparing vemurafenib with dacarbazine in patients with metastatic melanoma with the BRAF(V600E) mutation, vemurafenib improved rates of overall and progression-free survival in patients compared to dacarbazine.[78] In a phase II clinical trial with longer follow-up than the initially published data, the median overall survival was approximately 16 months.[79] The most common adverse events were arthralgia, rash, photosensitivity, fatigue, alopecia, and cutaneous squamous cell carcinomas in up to a quarter of patients.[79,80] Vemurafenib is now approved for treatment of BRAF-mutant metastatic melanoma, and several other BRAF inhibitors are in clinical trials. In light of positive results with concomitant BRAF and MEK inhibitors,[81] it is likely that this combination will be the next standard of care. An ongoing phase III clinical study is now evaluating this combination. Treatment of melanomas with mutations in the CKIT tyrosine kinase with imatinib leads to significant clinical responses.[82,83]

Immunotherapy

Interferon alfa has also been evaluated in the setting of metastatic disease, either alone or in combination with cytotoxic chemotherapy. Although it was associated with response rates up to 15%, complete responses were mostly in patients with limited, skin-only disease.[84] There is no benefit from the combination of cytotoxic chemotherapy and interferon.[85,86]

High-dose IL-2 induces objective responses in 12% to 21% of patients.[87] Strikingly, approximately 6% of patients have a durable complete response, with 59% of complete responders remaining progression-free at 7 years.[88] Due to the significant cardiopulmonary and toxicities associated with this treatment, patients need to be carefully selected.

Decreased immune system tolerance may contribute to progression of melanoma and other cancers, whereas inhibition of inhibitory immune "checkpoints," such as CTLA-4 (cytotoxic T-lymphocyte antigen 4) and PD-1 (programmed death 1)/PD-L1, may be a useful strategy for patients with melanoma.[89,90] The CTLA-4 antagonist ipilumimab was approved by the FDA on the bases of 2 large phase III clinical trials showing prolonged survival in patients with advanced melanoma. In the first study, patients who had received prior systemic treatment were randomized to ipilumimab or a glycoprotein 100 vaccine or both.[89] Ipilumimab was given every 3 weeks for 4 doses, and those who had partial or complete responses were allowed to receive their original treatment if they subsequently had disease progression. Patients with central nervous system disease were permitted in this trial. Immune-related events such as cutaneous reactions, pituitary dysfunction, hepatitis, and colitis can occur, but these can usually be managed with close surveillance and corticosteroids. In a second trial, patients who had no prior systemic treatment and no brain metastasis were randomized to ipilumimab plus dacarbazine or placebo plus dacarbazine.[91] Overall survival was significantly increased in patients assigned to ipilumimab plus dacarbazine compared with placebo plus dacarbazine. PD-1 blockage produced objec-

tive responses in melanoma[90] and remains an area of active further investigation.

CONCLUSION

In the United States, the incidence of melanoma is rising faster than any other malignancy without any corresponding decrease in mortality. Although many melanomas are diagnosed at early stages and can be cured with surgical excision, melanoma remains a vexing clinical problem, particularly in the setting of metastatic disease. With the recent advances in the molecular biology of this disease, it is hoped these new discoveries will be exploited for novel prevention and therapeutic strategies in the years to come.

BOARD REVIEW QUESTIONS

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