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Melanoma, Version 2.2013 : Featured Updates to the NCCN Guidelines

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NCCN Guidelines® Insights

Melanoma, Version 2.2013

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Melanoma provide multidisciplinary recommendations on the clinical management of patients with melanoma. This NCCN Guidelines Insights report highlights notable recent updates. Foremost of these is the exciting addition of the novel agents ipilimumab and vemurafenib for treatment of advanced melanoma. The NCCN panel also included imatinib as a treatment for KIT-mutated tumors and pegylated interferon alfa-2b as an option for adjuvant therapy. Also important are revisions to the initial stratification of early-stage lesions based on the risk of sentinel lymph node metastases, and revised recommendations on the use of sentinel lymph node biopsy for low-risk groups. Finally, the NCCN panel reached clinical consensus on clarifying the role of imaging in the workup of patients with melanoma. (*JNCCN* 2013;11:395–407)

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Disclosures for the NCCN Melanoma Panel

Individual disclosures of potential conflicts of interest for the NCCN Melanoma Panel members can be found on page 396.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the Panel's discussion, including the literature reviewed.**

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to NCCN Guidelines for Melanoma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Melanoma

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Disclosure of Affiliations and Significant Relationships

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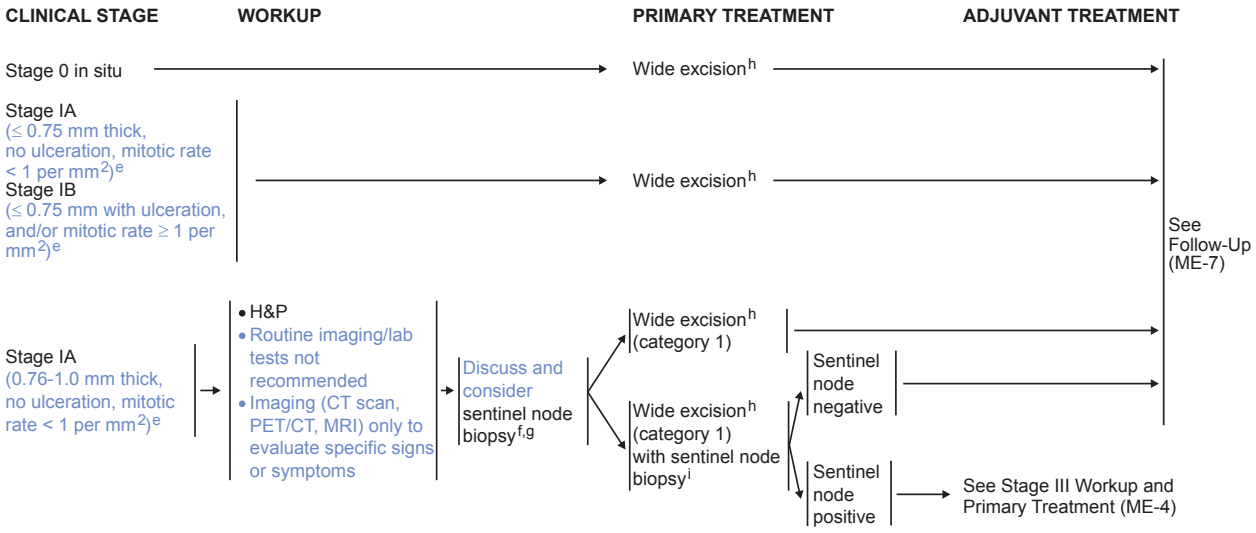

[e] In general, SLNB is not recommended for primary melanomas ≤ 0.75 mm thick, unless there is significant uncertainty about the adequacy of microstaging. For melanomas 0.76-1.0 mm thick, SLNB may be considered in the appropriate clinical context. In patients with thin melanomas (≤ 1.0 mm), apart from primary tumor thickness, there is little consensus as towhat should be considered "high-risk features" or a positive SLN. Conventional risk factors for a positive SLN, such as ulceration, high mitotic rate, and LVI, are very uncommon in melanomas ≤ 0.75 mm thick; when present, SLNB may be considered on an individual basis.

[f] Decision to perform SLNB may be based on significant patient comorbidities, patient preference or other factors.
[g] Sentinel node biopsy is an important staging tool, but the impact of SLNB on overall survival is unclear.
[h] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).
[i] Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

ME-2

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

In 2013, an estimated 76,690 new cases of melanoma will be diagnosed and approximately 9480 patients will die of the disease in the United States.[1] However, these figures for new cases may represent a substantial underestimate, because many superficial melanomas diagnosed and treated in the outpatient setting are not reported. The incidence of melanoma continues to increase dramatically. The lifetime risk of developing melanoma for someone born in the United States in 2005 may be as high as 1 in 55.[2] Although the outcome for thin localized lesions is excellent, the prognosis for advanced metastatic cases remains poor. Sentinel lymph node biopsy (SLNB) has emerged as an important staging tool that provides prognostic information. However, its clinical value in low-risk cases remains contentious.

Advances in cancer immunotherapy and molecular targeting in melanoma have yielded 2 novel agents, ipilimumab and vemurafenib, both of which

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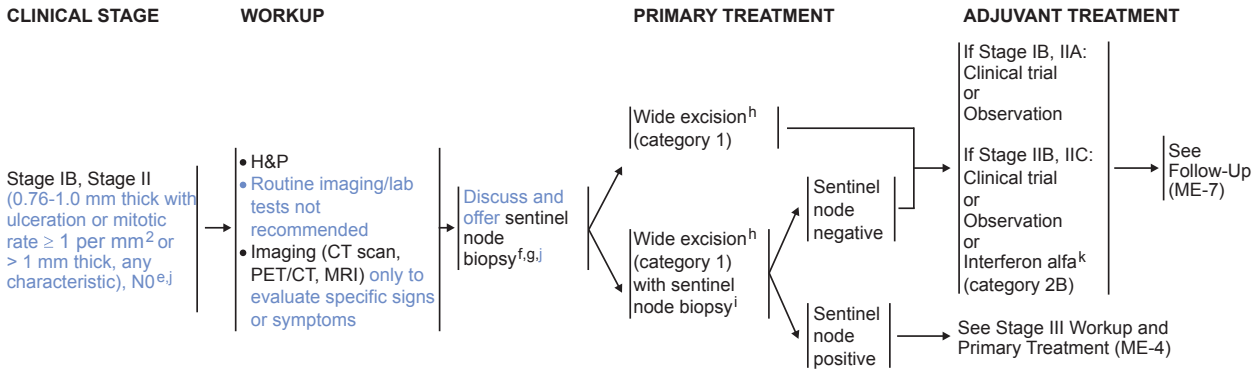

[e] In general, SLNB is not recommended for primary melanomas ≤ 0.75 mm thick, unless there is significant uncertainty about the adequacy of microstaging. For melanomas 0.76-1.0 mm thick, SLNB may be considered in the appropriate clinical context. In patients with thin melanomas (≤ 1.0 mm), apart from primary tumor thickness, there is little consensus as to what should be considered "high-risk features" for a positive SLN. Conventional risk factors for a positive SLN, such as ulceration, high mitotic rate, and LVI, are very uncommon in melanomas ≤ 0.75 mm thick; when present, SLNB may be considered on an individual basis.

[j] Microsatellitosis, when present in the initial biopsy or wide excision specimen, defines at least N2c and at least Stage IIIB disease. SLN status does have prognostic significance in these patients, with a positive SLN upstaging a patient to N3, Stage IIIC. However, the importance of SLNB in the management and outcome of these patients has not been clearly defined. Regardless of SLN status, these patients should be managed as Stage III in discussions of workup, adjuvant therapy, and follow-up.

[f] Decision to perform SLNB may be based on significant patient comorbidities, patient preference or other factors.
[g] Sentinel node biopsy is an important staging tool, but the impact of SLNB on overall survival is unclear.
[h] See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).
[i] Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.
[k] Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.

ME-3

have been shown to improve survival compared with historical standard therapy in patients with metastatic melanoma. The new hope they offer patients with advanced diseases is tempered by new questions and challenges, because each agent is associated with unique side effects and response patterns.

NCCN has assembled a multidisciplinary panel of leading experts from Member Institutions to develop and continually update guidelines for the treatment of melanoma. The full version of the latest guideline, including a complete list of updates, is available at NCCN.org. These NCCN Guidelines Insights highlight some of the recent major revisions. In addition to adding new therapeutic options for advanced disease, the NCCN Melanoma Panel made significant revisions to their recommendations on the use of SLNB in early-stage lesions, adjuvant interferon alfa-2b therapy for high-risk melanoma, and workup imaging. These updates are based on the dual commitment of the panel to provide useful treatment options and avoid unnecessary procedures.

SLNB

Similar to other malignancies, the prognosis for melanoma depends on whether the disease has spread beyond the primary site. SLNB is a minimally invasive staging procedure developed to identify patients with clinically localized melanoma with subclinical regional lymph node metastases who would be at higher risk of recurrence and who might be candidates for complete lymph node dissection or adjuvant systemic therapy. A large meta-analysis, including 71 studies and 25,240 participants, estimated the risk of nodal recurrence after a negative SLNB to be less than or equal to 5%.[3] However, ongoing controversy surrounds its routine use in melanoma, centered on its clinical benefit, cost, and potential downstream side effects.

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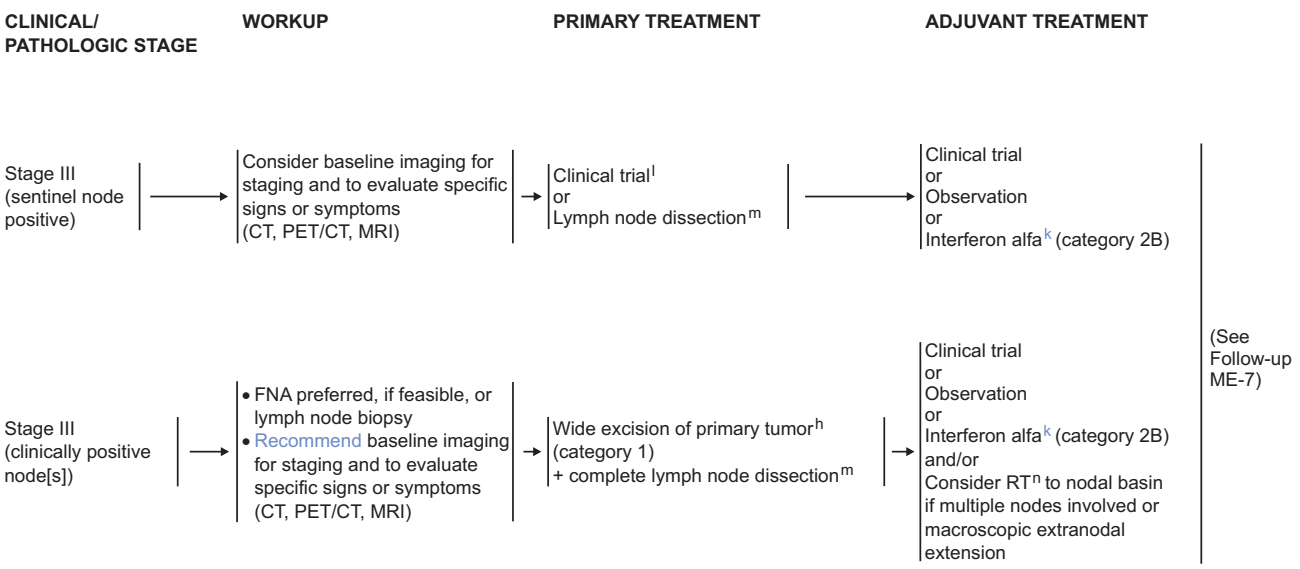


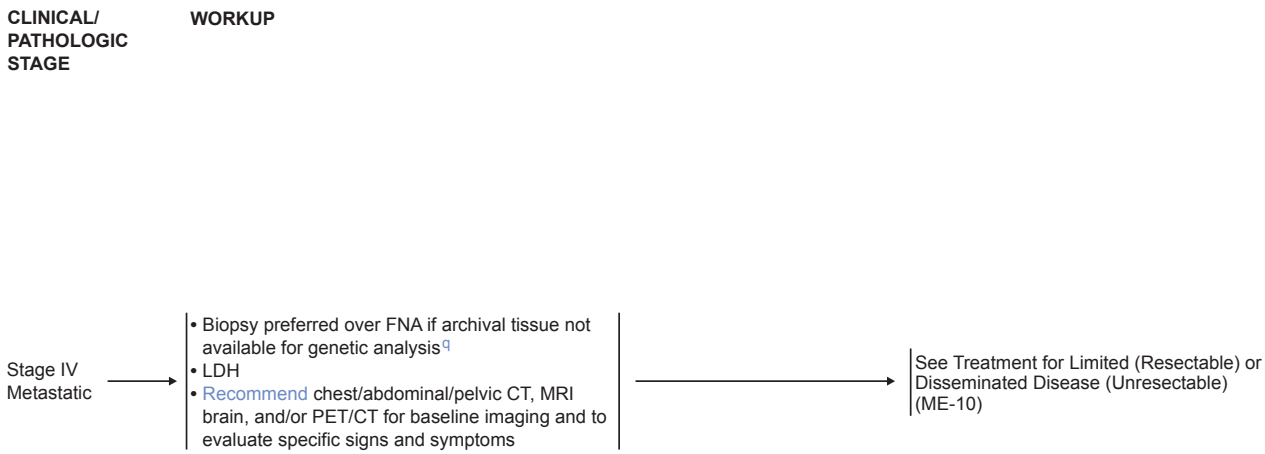
[h]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).
[k]Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been associated with improved DFS, but its impact on overall survival is unclear.
[l]Clinical trials assessing alternatives to complete lymph node dissection, such as careful observation with nodal basin ultrasound.
[m]See Principles of Complete Lymph Node Dissection (ME-C).
[n]See Principles of Radiation Therapy (ME-D).

ME-4

MSLT I (Multicenter Selective Lymphadenectomy Trial I), an international multicenter phase III trial, found SLNB to be an important staging tool in the initial assessment of patients with melanoma. The preliminary report of this trial clearly confirmed that SLN status was a strong independent predictor of outcome among patients with melanoma of intermediate thickness (1.2–3.5 mm). In addition, initial evaluation with SLNB was associated with an improvement in relapse-free but not disease-specific survival compared with wide excision alone.[5]

The value of SLNB for patients with thin melanomas (≤1.0 mm) and thick melanomas (≥4.0 mm) was not addressed specifically in the MSLTI trial. Because patients with thin melanoma have a generally favorable prognosis, the role of SLNB in this cohort is unclear.[6] A review by Andtbacka and Gershenwald[7] reported an overall sentinel lymph node (SLN) metastasis rate of 2.7% in patients with melanoma thinner than 0.75 mm from 7 studies. In patients with melanoma 0.75 to 1.0 mm thick, 6.2% of patients undergoing SLNB were found to have a positive SLN. Apart from increasing Breslow thickness, no other characteristics of thin primary melanomas consistently predicted an increased probability of a positive SLN. Furthermore, only one center has shown any convincing evidence that the SLN status was predictive of outcome in this low-risk group of patients.[8] Larger series and longer-term followup will be required to confirm the prognostic value of the SLN in patients with thin melanoma.[9–11]

The probability of a positive SLN in patients with thick melanoma (≥4 mm) is 30% to 40%. Almost every retrospective series has shown SLN status to be a strong independent predictor of outcome in patients with thick melanoma.[12–14] Thus, in these high-risk patients, it would seem reasonable to offer SLNB to help define prognostically homogeneous groups for participation in clinical trials of adjuvant therapy.



[q]Initial clinical recurrence should be confirmed pathologically whenever possible. Obtain tissue for genetic analysis from either archival material or biopsy of the metastasis if the patient is being considered for targeted therapy or if it is relevant to eligibility for participation in a clinical trial.

ME-6

NCCN Recommendations

The panel recognizes that the yield of SLNB depends principally on primary tumor characteristics, especially Breslow thickness. There is consensus that the procedure should be discussed and offered to patients with primary melanomas greater than 1.0 mm thick. Although panelists agreed that SLNB could provide some prognostic information for a small proportion of patients with very thin lesions (≤0.75 mm), most felt that the probability and clinical significance of SLN positivity are too low to justify this labor-intensive and expensive procedure in this cohort.

Revisions in the current guidelines reflect this consensus. Initial treatment of melanoma 1 mm or less in thickness is now based on the estimated risk of SLN metastasis (see ME-2 and ME-3, pages 397 and 398), rather than by AJCC stage. The presence of 1 mitosis/mm^2 or greater, which upstages a melanoma 1 mm or less in thickness from IA to IB, is no longer accepted by the panel as a primary indication to perform SLNB on patients with thin melanomas. In general, the panel does not recommend SLNB for melanoma that is 0.75 mm or less in thickness (see footnote e on ME-2 and ME-3, pages 397 and 398) Other than Breslow thickness, little consensus exists on what other conventional features, such as ulceration, high mitotic rate, and lymphovascular invasion, predict SLN positivity in thin melanomas. In the rare event that one of these features is present, the decision to perform SLNB should be left to the patient and the treating physician, acknowledging that data to inform this decision are scant. For melanomas 0.76 to 1.0 mm thick, SLNB should be discussed and considered. The discussion about SLNB in this group of patients should include the recognition that the yield of a positive SLNB is low and the clinical significance of a positive SLN is modest.

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SYSTEMIC THERAPY OPTIONS FOR ADVANCED OR METASTATIC MELANOMA

Preferred Regimens
- Ipilimumab (category 1)[1,2]
- Vemurafenib (category 1)[3,4]
- Clinical trial
- High-dose Interleukin-2[5,6]

Other Active Regimens
- Dacarbazine
- Temozolomide
- Imatinib for C-KIT mutated tumors
- Dacarbazine- or temozolomide-based combination chemotherapy/biochemotherapy, (including cisplatin and vinblastine with or without IL-2, interferon alfa) (category 2B)[6]
- Paclitaxel (category 2B)
- Paclitaxel/carboplatin (category 2B)

[1] Ipilimumab has the potential for significant immune-mediated complications. Participation in the risk evaluation and mitigation strategy (REMS) program and/or experience in use of the drug as well as resources to follow the patient closely are essential. Ipilimumab should be used with extreme caution, if at all, in patients with serious underlying autoimmune disorders.

[2] Re-induction with ipilimumab may be considered for select patients who experienced no significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or progress after stable disease > 3 months.

[3] Vemurafenib is recommended for patients with V600 mutation of the BRAF gene documented by an FDA-approved or Clinical Laboratory Improvement Amendments (CLIA)-approved facility.

[4] Vemurafenib has the potential for significant dermatologic complications including cutaneous squamous cell carcinoma and extreme photosensitivity. Regular dermatologic evaluation with referral to a dermatologist is recommended. Patients should also be carefully monitored for the development of other adverse reactions such as joint pain and swelling.

[5] High-dose interleukin-2 should not be used for patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. For patients with small brain metastases and without significant peritumoral edema, IL-2 therapy may be considered (category 2B).

[6] Administration of multiagent regimens and high-dose interleukin-2 is complex and associated with significant toxicities. Therapy should be restricted to an institution with medical staff experienced in the administration and management of these regimens.

ME-E (1 of 4)

The panel also discussed the role of SLNB in patients with microsatellitosis. Although SLN positivity would upstage the disease from N2b stage IIIB to N3 stage IIIC, its significance in treatment decisions and outcome has not been clearly defined (see footnote "j" on ME-3, on page 398).

In any patient who otherwise would be a candidate for SLNB, the decision to not perform SLNB may be based on significant patient comorbidities or individual patient preference.

Adjuvant Interferon Therapy

The goal of defining a safe and effective adjuvant therapy for patients with high-risk resected melanoma remains elusive. Much of the controversy in this realm centers on whether the optimal end point to define "effective" should be relapse-free or overall survival.

High-Dose Interferon

High-dose interferon alfa-2b, an immunomodulating cytokine, was approved by the FDA as adjuvant therapy for stage IIB–III melanoma in 1995. This approval was based on the pivotal ECOG 1684 trial that showed improved disease-free and overall survival with 1 year of interferon therapy compared with observation.[15] However, the overall survival benefit was not maintained at a longer follow-up of 12.6 years.[16] Toxicity was significant, with 67% of patients experiencing grade 3 toxicity during the course of therapy; 9% had life-threatening toxicity and 2 patients died from treatment. Approximately one-third of patients delayed or reduced treatment dosage because of toxicity issues. A larger follow-up trial (ECOG 1690) also showed a relapse-free survival advantage but no overall survival advantage.[17] Severe adverse events were again significant, with granulocytopenia and liver toxicity being the most

common, although no treatment-related deaths occurred. A pooled analysis confirmed an improvement in relapse-free survival in patients with high-risk resected melanoma (2-sided log-rank *P*=.006) without a corresponding significant improvement in overall survival.[16]

Pegylated Interferon

Pegylated interferon alfa-2b (also known as peginterferon alfa-2b) is a formulation of interferon conjugated to polyethylene glycol to improve circulation life and reduce immunogenicity. It was evaluated in the EORTC 18991 trial, which randomized 1256 patients with completely resected stage III melanoma (Tany,N1–2,M0, no in-transit metastases) to either observation or pegylated interferon for an intended duration of 5 years.[18] The 4-year relapse-free survival rate was significantly better in the interferon group compared with the observation group (45.6% vs 38.9%). However, no effect on overall survival was seen. Based on these data, pegylated interferon alfa received approval in 2011 as an option for adjuvant therapy for patients with melanoma with microscopic or gross nodal involvement. Its side effects profile is similar to that of the nonpegylated form; approximately one-third of patients discontinued treatment because of toxicity.

In a report on the long-term follow-up of EORTC 18991, the use of pegylated interferon was again associated with an improvement in relapse-free but not overall survival.[19] In a post hoc subset analysis of patients with stage III (microscopic nodal involvement) ulcerated melanoma, pegylated interferon was associated with an improvement in relapse-free and overall survivals. The theory that interferon therapy may be more effective in patients with ulcerated melanoma is currently being tested in EORTC 18081, a phase III trial comparing pegylated interferon alfa-2b versus observation in patients with node-negative ulcerated primary melanoma.[20]

NCCN Recommendations

The panel added pegylated interferon alfa-2b as an alternative to high-dose nonpegylated interferon for adjuvant treatment of completely resected stage III disease with either positive sentinel nodes or clinically positive nodes (see footnote "k" on ME-4, page 399)The use of adjuvant interferon with stage III in-transit disease has not been addressed in prospective randomized trials. Therefore, this decision has to be made on an individual basis. Both forms of interferon are category 2B recommendations. Pegylated interferon is prescribed for up to 5 years as opposed to high-dose nonpegylated interferon alfa which is given for up to 1 year.

Although panelists acknowledged that adjuvant high-dose interferon alfa-2b is a potentially toxic therapy, it may be indicated in select cases after careful consideration of the benefit-to-risk ratio. The NCCN category 2B designation is associated with either formulation of interferon, reflecting the nonuniform panel consensus on the value of this treatment. Decisions about the appropriateness of adjuvant interferon alfa-2b treatment for patients should be made on an individual basis after discussion with the patient, including an explanation of the potential benefits and side effects. The panel strongly encourages enrollment in clinical trials, because currently available options for adjuvant therapy have significant shortcomings.

New Therapies for Advanced Disease

The therapeutic landscape for advanced melanoma is evolving rapidly with the development of novel agents that have superior efficacy over traditional chemotherapy. Research is developing in 2 directions: immunotherapy and therapy targeted to specific tumor mutations.

Ipilimumab

Ipilimumab, a monoclonal antibody that binds to the immune-modulating receptor cytotoxic T lymphocyte antigen-4 (CTLA-4), received FDA approval for treatment of metastatic melanoma in 2011. Approval was based on results of a randomized phase III trial of 676 patients with unresectable metastatic disease that had progressed during systemic therapy.[21] Patients received ipilimumab plus a glycoprotein 100 peptide vaccine (gp100), ipilimumab alone, or gp100 alone. Overall survival was significantly longer in patients receiving the combination (10.0 months) or ipilimumab alone (10.1 months) compared with those receiving gp100 only (6.4 months). Notably, 15 of 23 patients who had experienced an initial response to ipilimumab without prohibitive toxicity and whose disease subsequently relapsed experienced partial response or stable disease after reinduction with the drug. Because ipilimumab stimulates T cells, it is associated with substantial risk of

immune-related reactions. Patients with underlying autoimmune disorders may be especially susceptible to serious reactions. In this pivotal trial, immune-related events were recorded in 60% of patients treated with the agent, with diarrhea being the most common. Seven deaths were attributed to immune-related toxicity.

A second phase III study conducted in patients with previously untreated metastatic melanoma also reported longer overall survival in those receiving dacarbazine plus ipilimumab than in those receiving dacarbazine plus placebo (11.2 vs. 9.1 months).[22] A 56% incidence of grade 3 or 4 adverse events was recorded in the ipilimumab arm, but no drug-related deaths occurred. Another open-label phase II study in 72 patients with melanoma and brain metastases reported a 24% disease control rate of the brain metastases in neurologically asymptomatic patients for whom steroid therapy was not required.[23] Overall response rates after administration of ipilimumab range from 10% to 20% and are often slow to manifest, sometimes occurring 6 months or more after initiation of therapy. The kinetics of response is important in selecting this agent for treating patients with metastatic melanoma.[23]

Given the potential for toxicity, ipilimumab approval was predicated on a risk evaluation and mitigation strategy (REMS). Familiarity with the adverse event profile of ipilimumab and early recognition and appropriate treatment of emerging adverse events are critical for the safe use of ipilimumab.

Vemurafenib

Approximately 45% of patients with metastatic melanoma harbor an activating mutation of the intracellular signaling kinase, BRAF. A randomized phase III trial compared vemurafenib, a BRAF-specific inhibitor, with dacarbazine in 675 patients with previously untreated metastatic melanoma containing a V600 mutation of BRAF was conducted.[24] Vemurafenib was associated with improved overall and progression-free survival (RR of death, 0.37; RR of death or progression, 0.26; $P<.001$). At 6 months, 84% and 64% of patients were alive in the vemurafenib and dacarbazine groups, respectively. Overall, 38% of patients receiving vemurafenib required dose modification because of adverse events. Skin complications were frequently associated with the agent, highlighting the importance of regular dermatologic evaluations while on treatment: 18% of vemurafenib-treated patients developed low-grade cutaneous squamous cell carcinomas or keratoacanthomas that required excision, whereas 12% experienced grade 2 or 3 photosensitivity skin reactions. Based on these results, vemurafenib was approved by the FDA in August 2011 for the treatment of *BRAF* mutation–positive unresectable or metastatic melanoma. Another phase II trial in 132 previously treated patients reported an overall response rate of 53% and a median survival of 15.9 months.[25] Secondary skin lesions were detected in 26% of patients. The Cobas 4800 BRAF V600 mutation test, a companion diagnostic test to determine the tumor mutational status, received approval along with the agent. Vemurafenib is not indicated for patients who do not have a mutation in the *BRAF* gene.

Imatinib

Advances in the molecular biology of melanoma have identified other therapeutic targets. *KIT* (commonly known as *c-kit*) mutations have been associated most commonly with mucosal and acral subtypes of melanoma.[26] Although less prevalent in Caucasian populations, these subtypes constitute approximately 65% of melanomas observed among Asians and African Americans. Somatic *KIT* mutations have been detected in 11% of Chinese patients with melanoma.[27] Imatinib is a tyrosine kinase inhibitor active against BCR-ABL in chronic myelogenous leukemia and mutated KIT in gastrointestinal stromal tumors. A phase II study of 43 patients with *KIT*-mutated metastatic melanomas showed a 23% overall response rate with imatinib therapy.[28] Unfortunately, most of these responses were of limited duration. Like vemurafenib, patient selection by molecular screening is essential to identify patients who might potentially benefit; previous studies on unselected patients yielded no meaningful responses.[29,30]

New Challenges

Although approval of ipilimumab and vemurafenib has significantly altered the initial management of patients with stage IV melanoma, each agent has unique limitations. For ipilimumab, the potential exists for serious autoimmune toxicity, clinical responses may take months to become apparent, and the overall response rate is less than 20%. However, responses, when seen, are often durable. Vemurafenib, on the other hand, is associated with a 40% to 50% response rate in patients with a V600-mutated *BRAF*

gene, and responses may be seen in days to weeks after starting the drug. Unfortunately, the median duration of response is only 5 to 6 months. The success of these 2 agents and their response patterns have engendered a series of new clinical trials investigating their use in the adjuvant setting, augmenting response by combining them with each other or with standard chemotherapy, and defining mechanisms of drug resistance.

NCCN Recommendations

The panel has reorganized systemic therapy options for advanced metastatic melanoma to reflect the recent advances (see ME-E 1 of 4, page 401). Although in principle NCCN encourages clinical trials, the discovery of 2 agents known to improve survival has prompted several discussions about how clinical trials should be prioritized in the guidelines. On one hand, the FDA-approved agents ipilimumab and vemurafenib have, for the first time, demonstrated improved survival in these patients. On the other hand, with the unprecedented intensity and speed of melanoma research, patients may benefit even more from enrolling in clinical trials of other exciting new treatments, such as the BRAF-inhibitor dabrafenib, MEK-inhibitor trametinib, anti-PD-1 therapy, or combination therapy.[31–35] The final consensus was to create a "preferred regimens" category to include ipilimumab (category 1), vemurafenib (category 1), clinical trial, and high-dose interleukin-2. Footnotes on potential complications and special monitoring of ipilimumab and vemurafenib have also been added (see footnotes "1" and "4" on ME-E 1 of 4, page 401). Imatinib is an added option under "other active regimens," specifically for the relatively uncommon *KIT*-mutated cases.

The panel recognized the increasing importance of potentially actionable mutations that may help direct therapy. Documented mutation of a specific gene may be necessary for routine clinical care decisions or for participation in clinical trials of target-specific agents. Clinicians are advised to obtain tissue for genetic analysis if a patient with recurrent or advanced melanoma or recurrence is being considered for targeted therapy (see footnote "q" on ME-6, page 400). Beyond that specific clinical indication, the panel currently does not endorse routine testing for genetic mutations on primary localized melanomas, because the results have no known immediate prognostic or therapeutic implications.

Although the BRAF inhibitor clinical trials primarily enrolled patients with the V600E mutation, patients with other V600 mutations such as V600K were also included.[24,25] Hence, the panel recommends consideration of vemurafenib for patients with a documented V600 mutation (see footnote "3" on ME-E 1 of 4, page 401). Mutational status should be tested by an FDA-approved test or a facility approved by Clinical Laboratory Improvement Amendments (CLIA). Likewise, panelists agreed that imatinib therapy is only appropriate for patients with *KIT* mutations.

Reinduction with ipilimumab is an emerging issue, which is likely to become increasingly important with greater experience with the drug. The panelists agreed that this is a reasonable option to consider in patients whose disease relapsed or progressed after having experienced tumor shrinkage or stable disease for at least more than 3 months without significant toxicity from prior ipilimumab therapy (see footnote "2" on ME-E 1 of 4, page 401).

Imaging

Several reasons exist to embark on an extent-of-disease workup in patients with melanoma. One is to establish a set of baseline images against which to compare future studies in a patient at risk for relapse. Another is to detect clinically occult disease that would affect immediate treatment decisions. A third reason is to define homogeneously staged patients for inclusion in clinical trials. Although patients greatly value the negative result of a cross-sectional imaging study, physicians must be cautious about overinterpreting the significance of the findings, recognizing that all tests have relatively insensitive lower limits of resolution. Finally, any test that is ordered has with it the very real possibility of detecting findings unrelated to the melanoma, findings that could lead to morbid biopsy procedures and excessive patient anxiety.

The yield of routine imaging in screening patients with stage I–II melanoma for asymptomatic distant metastatic disease is very low. Findings of cross-sectional imaging are often nonspecific, with frequent false-positive findings unrelated to melanoma.[36–38] The yield of imaging studies has been more extensively evaluated in the context of patients with stage III melanoma. In patients with a positive SLN,

the yield of crosssectional imaging in detecting clinically occult distant metastatic disease ranges from 0.5% to 3.7%.[39–42] True-positive findings are most often found in patients with ulcerated thick primary tumors and those with a large tumor burden in their sentinel nodes. In asymptomatic patients with clinically positive nodes, the yield of routine cross-sectional imaging is a bit higher than in those with positive sentinel nodes, reported at 4% to 16%.[43–45] All of these series also report a significant incidence of indeterminate or false-positive radiologic findings that are unrelated to the melanoma.

These retrospective studies are reporting minimum estimates, because a study population of patients with truly "imaging naïve" stage III disease is very difficult to define. It is probable that, among the entire denominator of patients with stage III disease, some would have been defined as having stage IV disease based on imaging before the study cohort was assembled. Furthermore, because a significant proportion of patients with clinical stage III disease will ultimately develop distant metastases, the inability of cross-sectional imaging studies to detect metastatic disease at diagnosis of stage III disease is a relatively poor predictor of future events.

PET/CT scanning has attracted interest as a means of enhancing detection of subclinical metastatic disease. Most investigators have described very low yield and poor sensitivity in detecting metastatic disease in patients with clinically localized melanoma.[46–48] In patients with more advanced stage III disease, PET/CT scanning may be more useful either for initial screening for metastases, or for further characterizing lesions found to be indeterminate on CT scan. Another potential advantage of PET/CT is that it can image areas not included in routine body CT scans.[49,50]

NCCN Recommendations

As part of a continuous effort to minimize unnecessary imaging procedures, the panel discussed which should be included in the workup of patients with melanoma. Practices among the NCCN Member Institutions vary greatly. In the absence of compelling data beyond the retrospective series cited earlier, recommendations for the appropriate extent of imaging workup are predominantly based on general consensus within the panel. Guideline updates clarified that routine cross-sectional imaging is not recommended for patients with stage I and II melanoma (see ME-2 and ME-3, pages 397 and 398). These tests should only be used to investigate specific signs or symptoms.

Most panel members acknowledged the low yield of screening CT or PET/CT scans in patients with stage III melanoma. Based on the results of the studies reported in the literature and the absence of conclusive data, the panel left the extent of cross-sectional imaging to the discretion of the treating physician. In the case of positive SLNB findings, baseline imaging remains a consideration. For patients presenting with clinically positive nodes or in-transit metastases or recurrence, "consider" has been revised to "recommend," because most of the panel endorsed baseline imaging for staging purposes and to evaluate specific signs or symptoms (see ME-4 as an example, page 399). At a minimum, a pelvic CT scan is recommended in the setting of inguinofemoral lymphadenopathy to rule out associated pelvic or retroperitoneal nodal involvement. Consensus is universal that imaging is important for patients presenting with stage IV disease (see ME-6, page 400).

Conclusions

Important updates to the management of melanoma in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma are highlighted in this report. The NCCN Guidelines are updated at least annually, and more often when new high-quality clinical data become available in the interim. The most up-to-date version of these continuously evolving guidelines is available online at NCCN.org. The recommendations in the NCCN Guidelines are based on evidence from clinical trials when available, combined with expert consensus of the NCCN Melanoma Panel. Independent medical judgment is required to apply these guidelines individually to provide optimal care. The physician and patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages participation in prospective clinical trials.

References

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.

2. National Cancer Institute. Surveillance Epidemiology and End Results. 2008. Available at: http://seer.cancer.gov/statfacts/html/melan.html#ref11. Accessed January 10, 2013.
3. Valsecchi ME, Silbermins D, de Rosa N, et al. Lymphatic mapping and sentinel lymph node biopsy in patients with melanoma: a meta-analysis. J Clin Oncol 2011;29:1479–1487.
4. Torjesen I. Sentinel node biopsy for melanoma: unnecessary treatment? BMJ 2013;346:e8645.
5. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med 2006;355:1307–1317.
6. Thompson JF, Shaw HM. Sentinel node mapping for melanoma: results of trials and current applications. Surg Oncol Clin N Am 2007;16:35–54.
7. Andtbacka RH, Gershenwald JE. Role of sentinel lymph node biopsy in patients with thin melanoma. J Natl Compr Canc Netw 2009;7:308–317.
8. Wright BE, Scheri RP, Ye X, et al. Importance of sentinel lymph node biopsy in patients with thin melanoma. Arch Surg 2008;143:892–899; discussion 899–900.
9. Bleicher RJ, Essner R, Foshag LJ, et al. Role of sentinel lymphadenectomy in thin invasive cutaneous melanomas. J Clin Oncol 2003;21:1326–1331.
10. Ranieri JM, Wagner JD, Wenck S, et al. The prognostic importance of sentinel lymph node biopsy in thin melanoma. Ann Surg Oncol 2006;13:927–932.
11. Wong SL, Brady MS, Busam KJ, Coit DG. Results of sentinel lymph node biopsy in patients with thin melanoma. Ann Surg Oncol 2006;13:302–309.
12. Ferrone CR, Panageas KS, Busam K, et al. Multivariate prognostic model for patients with thick cutaneous melanoma: importance of sentinel lymph node status. Ann Surg Oncol 2002;9:637–645.
13. Gershenwald JE, Mansfield PF, Lee JE, Ross MI. Role for lymphatic mapping and sentinel lymph node biopsy in patients with thick (> or = 4 mm) primary melanoma. Ann Surg Oncol 2000;7:160–165.
14. Gutzmer R, Satzger I, Thoms KM, et al. Sentinel lymph node status is the most important prognostic factor for thick (> or = 4 mm) melanomas. J Dtsch Dermatol Ges 2008;6:198–203.
15. Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 1996;14:7–17.
16. Kirkwood JM, Manola J, Ibrahim J, et al. A pooled analysis of Eastern Cooperative Oncology Group and Intergroup trials of adjuvant high-dose interferon for melanoma. Clin Cancer Res 2004;10:1670–1677.
17. Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of Intergroup trial E1690/S9111/C9190. J Clin Oncol 2000;18:2444–2458.
18. Eggermont AM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. Lancet 2008;372:117–126.
19. Eggermont AM, Suciu S, Testori A, et al. Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. J Clin Oncol 2012;30:3810–3818.
20. National Institutes of Health. Adjuvant PEG intron in ulcerated melanoma (clinical trial). Available at: http://clinicaltrials.gov/show/NCT01502696. Accessed January 10, 2013.
21. Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–723.
22. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–2526.
23. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012;13:459–465.
24. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364:2507–2516.
25. Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012;366:707–714.
26. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 2006;24:4340–4346.
27. Si L, Guo J. C-kit-mutated melanomas: the Chinese experience. Curr Opin Oncol 2013;25:160–165.
28. Guo J, Si L, Kong Y, et al. Phase II, open-label, single-arm trial of imatinib mesylate in patients with metastatic melanoma harboring c-Kit mutation or amplification. J Clin Oncol 2011;29:2904–2909.
29. Wyman K, Atkins MB, Prieto V, et al. Multicenter Phase II trial of high-dose imatinib mesylate in metastatic melanoma: significant toxicity with no clinical efficacy. Cancer 2006;106:2005–2011.
30. Ugurel S, Hildenbrand R, Zimpfer A, et al. Lack of clinical efficacy of imatinib in metastatic melanoma. Br J Cancer 2005;92:1398–1405.
31. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455–2465.
32. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358–365.
33. Flaherty KT, Infante JR, Daud A, et al. Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 2012;367:1694–1703.
34. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 2012;367:107–114.
35. Di Giacomo AM, Ascierto PA, Pilla L, et al. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. Lancet Oncol 2012;13:879–886.
36. Buzaid AC, Sandler AB, Mani S, et al. Role of computed tomography in the staging of primary melanoma. J Clin Oncol 1993;11:638–643.
37. Wang TS, Johnson TM, Cascade PN, et al. Evaluation of staging chest radiographs and serum lactate dehydrogenase for localized melanoma. J Am Acad Dermatol 2004;51:399–405.
38. Yancovitz M, Finelt N, Warycha MA, et al. Role of radiologic imaging at the time of initial diagnosis of stage T1b-T3b melanoma. Cancer 2007;110:1107–1114.
39. Aloia TA, Gershenwald JE, Andtbacka RH, et al. Utility of computed tomography and magnetic resonance imaging staging before completion lymphadenectomy in patients with sentinel lymph node-positive melanoma. J Clin Oncol 2006;24:2858–2865.
40. Gold JS, Jaques DP, Busam KJ, et al. Yield and predictors of radiologic studies for identifying distant metastases in melanoma

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patients with a positive sentinel lymph node biopsy. Ann Surg Oncol 2007;14:2133–2140.

41. Miranda EP, Gertner M, Wall J, et al. Routine imaging of asymptomatic melanoma patients with metastasis to sentinel lymph nodes rarely identifies systemic disease. Arch Surg 2004;139:831-836; discussion 836–837.
42. Pandalai PK, Dominguez FJ, Michaelson J, Tanabe KK. Clinical value of radiographic staging in patients diagnosed with AJCC stage III melanoma. Ann Surg Oncol 2011;18:506–513.
43. Buzaid AC, Tinoco L, Ross MI, et al. Role of computed tomography in the staging of patients with local-regional metastases of melanoma. J Clin Oncol 1995;13:2104–2108.
44. Johnson TM, Fader DJ, Chang AE, et al. Computed tomography in staging of patients with melanoma metastatic to the regional nodes. Ann Surg Oncol 1997;4:396–402.
45. Kuvshinoff BW, Kurtz C, Coit DG. Computed tomography in evaluation of patients with stage III melanoma. Ann Surg Oncol 1997;4:252–258.
46. Clark PB, Soo V, Kraas J, et al. Futility of fluorodeoxyglucose F 18 positron emission tomography in initial evaluation of patients with T2 to T4 melanoma. Arch Surg 2006;141:284–288.
47. Maubec E, Lumbroso J, Masson F, et al. F-18 fluorodeoxy-D-glucose positron emission tomography scan in the initial evaluation of patients with a primary melanoma thicker than 4 mm. Melanoma Res 2007;17:147–154.
48. Wagner JD, Schauwecker D, Davidson D, et al. Inefficacy of F-18 fluorodeoxy-D-glucose-positron emission tomography scans for initial evaluation in early-stage cutaneous melanoma. Cancer 2005;104:570–579.
49. Brady MS, Akhurst T, Spanknebel K, et al. Utility of preoperative [(18)]f fluorodeoxyglucose-positron emission tomography scanning in high-risk melanoma patients. Ann Surg Oncol 2006;13:525–532.
50. Xing Y, Bronstein Y, Ross MI, et al. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. J Natl Cancer Inst 2011;103:129–142.

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Posttest Questions

1. True or False: According to the NCCN Melanoma Panel, SLNB should be discussed and offered as a procedure for patients with stage II melanoma.
2. True or False: To date, ipilimumab and vemurafenib have not demonstrated improved survival in patients with advanced metastatic melanoma.
3. True or False: The NCCN Melanoma Panel added pegylated interferon alfa-2b as an alternative to high-dose nonpegylated interferon for adjuvant treatment of completely resected stage III disease with either positive sentinel nodes or clinically positive nodes.