NCCN Guidelines® Insights

Melanoma, Version 4.2014

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Melanoma provide multidisciplinary recommendations for the management of patients with melanoma. These NCCN Guidelines Insights highlight notable recent updates. Dabrafenib and trametinib, either as monotherapy (category 1) or combination therapy, have been added as systemic options for patients with unresectable metastatic melanoma harboring *BRAF* V600 mutations. Controversy continues regarding the value of adjuvant radiation for patients at high risk of nodal relapse. This is reflected in the category 2B designation to consider adjuvant radiation following lymphadenectomy for stage III melanoma with clinically positive nodes or recurrent disease. (*J Natl Compr Canc Netw* 2014;12:621–629)

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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

Disclosure of Relevant Financial Relationships

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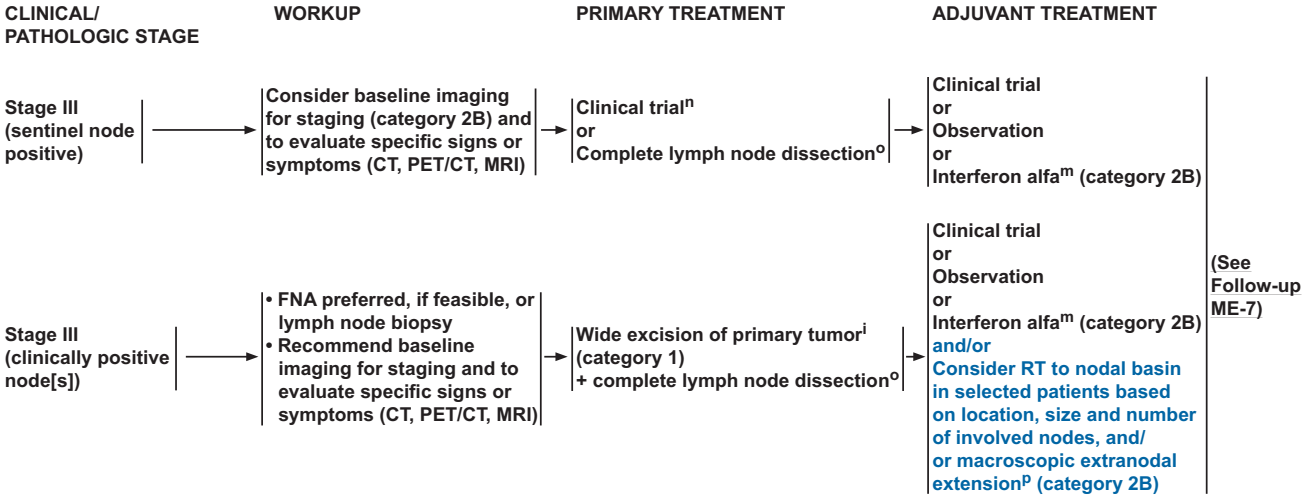


[i]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B).
[m]Interferon can be given as high-dose alfa interferon for one year or as peginterferon alfa-2b for up to 5 years. Adjuvant interferon has been shown to improve DFS (category 1); its impact on overall survival remains unclear (category 2B).
[n]Clinical trials assessing alternatives to complete lymph node dissection, such as careful observation with nodal basin ultrasound.
[o]See Principles of Complete Lymph Node Dissection (ME-C).
[p]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has no impact on relapse-free or overall survival, and its benefits must be weighed against the increased probability of long-term skin and regional toxicities and potential reduced quality of life. See Principles of Radiation Therapy for Melanoma (ME-D).

ME-4

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.

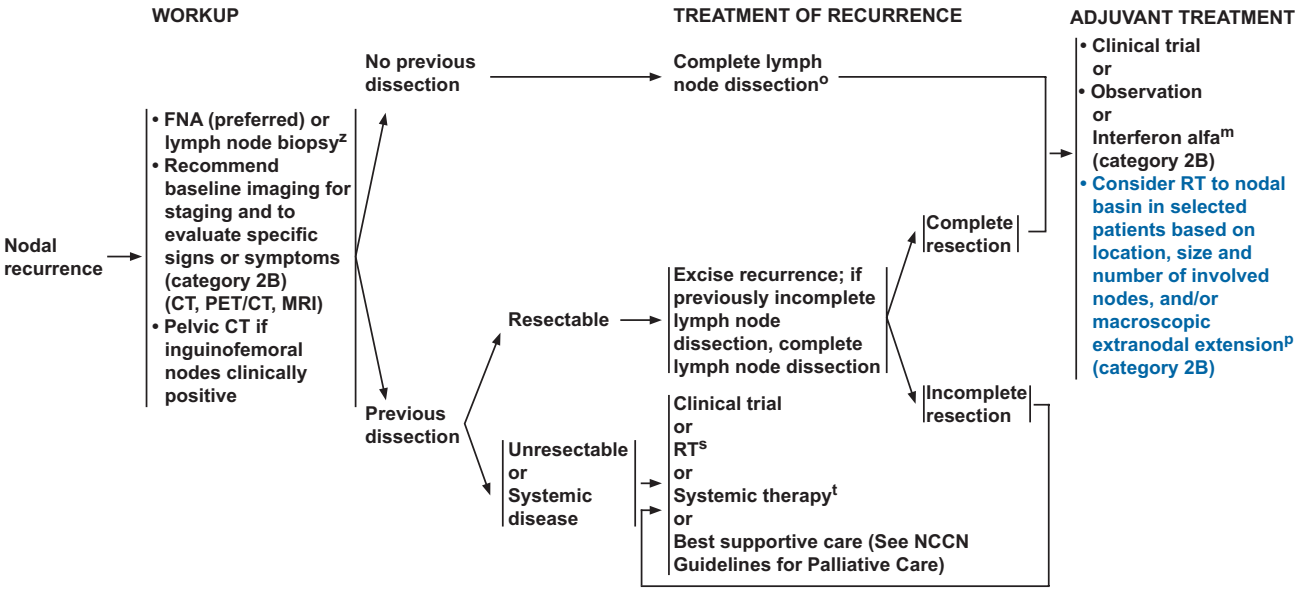
All recommendations are category 2A unless otherwise noted.

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

Melanoma remains one of the most aggressive malignancies. In 2014, an estimated 76,100 new cases of melanoma will be diagnosed and approximately 9710 patients will die of the disease in the United States.[1] The incidence of melanoma continues to increase dramatically at an overall rate of 33% and 23% for men and women from 2002 to 2006, respectively.[2] Although patients with early-stage melanoma have a good prognosis after excision, patients with stage III disease have a heightened risk of recurrence. The role of adjuvant radiation therapy (RT) to reduce nodal relapse is a source of ongoing controversy because of the lack of survival benefits and concerns of late toxicities.

With the advent of targeted therapy for advanced melanoma, there is increasing appreciation that the incidence of specific genetic alterations differs among melanoma subtypes. For example, melanoma on nonchronic sun damaged (non-CSD) areas



[m]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 shown to improve DFS (category 1); its impact on overall survival remains unclear (category 2B).
[o]See Principles of Complete Lymph Node Dissection (ME-C).
[p]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has no impact on relapse-free or overall survival, and its benefits must be weighed against the increased probability of long-term skin and regional toxicities and potential reduced quality of life. See Principles of Radiation Therapy for Melanoma (ME-D).
[s]See Principles of Radiation Therapy for Melanoma (ME-D).
[t]See Systemic Therapy Options for Advanced or Metastatic Melanoma (ME-E).
[z]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-9

was found to have the highest proportion of *BRAF* mutations (56%) compared with CSD, acral, and mucosal lesions (6%, 21%, and 3%, respectively).[3] Treatment options for patients harboring *BRAF* V600 mutations are increasing with the approval of additional targeted inhibitors, dabrafenib and trametinib. However, because of the rapid development of therapeutic resistance after initial dramatic responses to targeted monotherapy, combination targeted therapy is emerging as a logical approach.

NCCN has assembled a multidisciplinary panel of leading experts from NCCN Member Institutions to develop and continually update guidelines for the treatment of melanoma. The most recent complete guideline, including a list of updates, is available on the NCCN Web site at NCCN.org. The following sections of these NCCN Guidelines Insights highlight some of the recent major revisions to the melanoma guidelines, including revised recommendations for the use of adjuvant RT and additions of targeted therapeutic options for *BRAF*-mutated advanced melanoma.

Adjuvant RT

The safety and effectiveness of adjuvant nodal basin RT for patients with high-risk resected melanoma remain controversial. The largest retrospective review examining the role of RT was performed by Agrawal et al,[4] who evaluated 615 patients who met the specific criteria portending a "high risk" of regional nodal relapse based on lymph node number, size, location, and extracapsular extension. At a median follow-up of 5 years, regional recurrence occurred in 10.2% of the radiated patients compared with 40.6% of the nonradiated patients. Interpretation of these results should take into consideration selection bias and many other potential forms of bias inherent in retrospective studies. Adjuvant radiation was associated with improved locoregional control on mul-

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PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Consider RT in the following situations:[1]

PRIMARY DISEASE

- **Adjuvant treatment in selected patients with desmoplastic melanoma with narrow margins, locally recurrent disease, or extensive neurotropism.**

REGIONAL DISEASE[2]

- **Adjuvant treatment in selected patients following resection of clinically appreciable nodes (category 2B)[3] if**
  - **LDH <1.5 x upper limit of normal AND**
  - **Gross nodal extracapsular extension AND/OR**
    - **Parotid: ≥1 involved node, any size of involvement**
    - **Cervical: ≥2 involved nodes and/or ≥3 cm tumor within a node**
    - **Axillary: ≥2 involved nodes and/or ≥4 cm tumor within a node**
    - **Inguinal: ≥3 involved nodes and/or ≥4 cm tumor within a node**
- **Palliative**
  - **Unresectable nodal, satellite, or in-transit disease**

METASTATIC DISEASE

- **Brain metastases (see NCCN Guidelines for Central Nervous System Cancers)**
  - **Stereotactic radiosurgery and/or whole brain radiation therapy either as adjuvant or the primary treatment**
- **Other symptomatic or potentially symptomatic soft tissue and/or bone metastases[2]**

[1]Interactions between radiation therapy and systemic therapies need to be very carefully considered.
[2]A wide range of radiation dose/fractionation schedules is effective. Hypofractionated regimens may increase the risk for long-term complications.
[3]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has no impact on relapse-free or overall survival, and its benefits must be weighed against the increased probability of long-term skin and regional toxicities and potential reduced quality of life.

ME-D (1 OF 2)

tivariate analysis (P<.0001). However, treatment-related morbidity was significantly increased with RT (5-year rate, 20% vs 13%; P=.004), particularly lymphedema.

A phase III, prospective, randomized trial of adjuvant nodal basin RT versus observation was conducted by the Australian and New Zealand Melanoma Trials Group and Trans Tasman Radiation Oncology Group (ANZMTG 01.02/TROG 02.01) in 250 patients at risk for nodal relapse. Patients with nonmetastatic disease with palpable lymphadenopathy at diagnosis or as an isolated site of relapse underwent therapeutic lymph node dissection followed by either adjuvant radiation to the nodal basin or observation.[5] Eligible patients were required to have a lactate dehydrogenase (LDH) level less than 1.5 times the upper limit of normal; 1 or more parotid, 2 or more cervical or axillary, or 3 or more groin positive nodes; a maximum nodal diameter of 3 cm or greater in the neck, or 4 cm or greater in the axilla or groin; or nodal extracapsular extension. Patients with nodal involvement detected by sentinel lymph node biopsy were not eligible. At a median follow-up of 40 months, lymph node field recurrence was significantly less frequent in the adjuvant radiation group (hazard ratio [HR], 0.56; 95% CI, 0.32–0.98; P=.041) for all nodal basins, but relapse-free survival was not improved. Although not statistically significant, a trend was seen toward improved overall survival in the observation group. In the final analysis (mean follow-up, 73 months) reported in abstract form, locoregional symptoms were higher in the RT group (P=.035).[6] Adjuvant radiation was also associated with frequent grade 2 to 4 long-term toxicities in the head and neck (33%), axilla (41%–44%), and groin (38%–67%). Quality of life was statistically similar in both groups.

The NCCN Melanoma Panel has discussed at length the value of adjuvant RT in patients at high risk of recurrence. Panelists agree that high-level

SYSTEMIC THERAPY OPTIONS FOR ADVANCED OR METASTATIC MELANOMA

Preferred Regimens	Other Active Regimens
• Ipilimumab (category 1)[1,2]	• Trametinib (category 1)[3,9]
• Vemurafenib (category 1)[3,4]	• Imatinib for C-KIT mutated tumors
• Dabrafenib (category 1)[3,5]	• Dacarbazine
• Dabrafenib + trametinib[3,6]	• Temozolomide
• Clinical trial	• Albumin-bound paclitaxel
• High-dose IL-2[7,8]	• Dacarbazine- or temozolomide-based combination chemotherapy/biochemotherapy (including cisplatin and vinblastine with or without IL-2, interferon alfa) (category 2B)[8]
	• 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, dabrafenib, and trametinib are recommended only 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 educated to report the development of other adverse reactions such as joint pain and swelling.

[5]Dabrafenib administration can be associated with significant episodic and recurrent fevers that should be managed by discontinuation of dabrafenib and institution of anti-pyretics such as acetaminophen and/or NSAIDs. Dabrafenib is associated with keratoacanthoma/low grade squamous carcinomas and little if any significant photosensitivity. Regular dermatologic evaluation and referral to a dermatologist is recommended. Patients should also be educated to report the development of other adverse reactions such as joint pain and swelling.

[6]The combination of dabrafenib with trametinib was associated with improved progression-free survival (PFS) compared to dabrafenib monotherapy in a phase I/II trial; however, improvement in overall survival has not been demonstrated. Combination therapy may be associated with less cutaneous toxicity than monotherapy.

[7]High-dose IL-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).

[8]Administration of multiagent regimens and high-dose IL-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.

[9]Single-agent trametinib is not indicated for the treatment of patients who have experienced progression of disease on prior *BRAF* inhibitor therapy. Single-agent trametinib can be used for the treatment of *BRAF*-mutated melanoma in patients who are intolerant to single-agent *BRAF* inhibitors.

ME-E (1 OF 4)

evidence indicates that adjuvant RT is useful in preventing nodal relapse. However, some institutions argued that the increased late toxicity associated with RT can potentially be detrimental to quality of life, and hence defeats the purpose of preventing morbidity associated with recurrence. This was coupled with concerns regarding the lack of survival benefits, including a trend toward worse overall survival in the RT arm (HR, 1.37; 95% CI, 0.94–2.01; *P*=.12). It is possible that the difference may become significant at longer follow-up. Because overall survival was not the primary end point, the study was underpowered for a definitive conclusion. On the other hand, some panelists found that the benefit of reducing nodal recurrence and related complications can outweigh radiation-associated morbidity in certain circumstances (such as in the neck region). Therefore, maintaining adjuvant RT as an option may be helpful.

Postsurgical RT with various fractionation schemes have been used in other clinical studies.[7–9] Hypofractionated RT appears as equally effective as standard fractionation. Although particular concern for toxicity should be exercised when using higher doses per fraction, all studied regimens seem to be similarly tolerated.

Some systemic therapy regimens may increase toxicity when given concurrently with RT. For example, patients with surgically resected stage III melanoma receiving concurrent adjuvant RT and interferon alfa experienced significant toxicity.[10] On the other hand, studies have shown the safety of combining temozolomide with RT when treating brain metastases.[11,12]

NCCN Recommendations

Consideration of adjuvant RT after lymphadenectomy is a category 2B recommendation for select patients with stage III disease and clinically positive nodes (does not include patients with nodal metastasis detected by sentinel node biopsy) or recurrent disease (see ME-4 and ME-9, pages 623 and 624),

reflecting a lack of uniform panel consensus on its value. The panel recognized that adjuvant RT may not be appropriate for many patients, and emphasized that it is included as an option for select cases, not as a mandatory recommendation. Careful patient selection based on location, size, number of positive nodes, and extranodal extension is critical (ME-D 1 of 2, page 625). The benefits of adjuvant RT must be weighed against the increased likelihood of long-term skin and regional toxicities that can affect quality of life. Careful consideration should be given to potential interactions between RT and systemic therapy.

New Targeted Therapies

Approximately half of patients with metastatic melanoma harbor an activating mutation of the intracellular signaling kinase BRAF, mainly at codon 600.[13] This results in constitutive activation of the MAPK signalling pathway that regulates cellular proliferation, differentiation, cell survival, and apoptosis. Most *BRAF* mutations are V600E (>70%), with the V600K genotype being the next most common (≈20%).

This paradigm-changing molecular discovery of *BRAF* mutations has led to the development of targeted inhibitors that induce survival benefits. After the success of first-in-class *BRAF* inhibitor vemurafenib, 2 additional agents targeting *BRAF*-mutated disease have been approved. These new agents not only widen the choice of targeted monotherapy but also make possible the emerging strategy of combining targeted agents.

The THxID-BRAF test, a companion genetic test for the V600E or V600K *BRAF* mutation, has received approval along with dabrafenib and trametinib.

Dabrafenib

Like vemurafenib, dabrafenib is an oral selective BRAF inhibitor. The pivotal, open-label, phase III trial randomized 250 patients with untreated stage IV or unresectable stage III melanoma harboring the *BRAF* V600E mutation to receive dabrafenib or dacarbazine.[14] The primary end point was progression-free survival, which was reached, with dabrafenib resulting in 5.1 versus 2.7 months for dacarbazine (HR, 0.30; 95% CI, 0.18–0.51; *P*<.0001). Grade 2 or higher adverse events occurred in 53% of patients receiving dabrafenib, although grade 3 or 4 events were uncommon. The most frequent side effects were skin-related toxicity, fever, fatigue, arthralgia, and headache. Compared with vemurafenib, dabrafenib was associated with less cutaneous squamous cell carcinoma or keratoacanthoma (6%), and phototoxic reactions were rare; however, pyrexia may be a concern (11%).

Dabrafenib also demonstrated intracranial activity in a phase II study of 172 patients with *BRAF*-mutated (V600E/K) melanoma and asymptomatic brain metastases.[15] An overall intracranial response was experienced by 39% and 31% of previously untreated and treated patients, respectively.

Trametinib

Trametinib is an oral small-molecule inhibitor of MEK1 and MEK2, which are downstream of BRAF in the MAPK signal transduction pathway. A phase III open-label study randomly assigned 322 patients with metastatic melanoma to trametinib or chemotherapy.[16] All participants had V600E or V600K *BRAF* mutations. Compared with the chemotherapy group, patients in the trametinib arm showed improved progression-free survival (4.8 vs 1.5 months; HR, 0.45; 95% CI, 0.33–0.63; *P*<.001) and 6-month overall survival (81% vs. 67%; HR, 0.54; 95% CI, 0.32–0.92; *P*=.01). The most common side effects associated with trametinib include rash, diarrhea, and peripheral edema. Most adverse events were mild and did not require discontinuation of treatment. Unlike BRAF inhibitors, trametinib was not associated with secondary skin lesions.

In an open-label phase II study, trametinib failed to demonstrate objective responses in 40 patients previously treated with a BRAF inhibitor.[17] Compared to BRAF inhibitors, trametinib is associated with a lower response rate in previously untreated patients (22% vs. 48%–50%).[16,18,19]

Combined Targeted Therapies

Despite high initial response rates, half of the patients treated with targeted monotherapies experience relapse within approximately 6 months.[16,19,20] Combination therapy offers the potential to augment response and delay resistance through reactivation of the MAPK cascade. In addition, the development of secondary squamous cell carcinomas during BRAF inhibition is associated with paradoxical MAPK activation.[21] In a mouse model, this effect was sup-

pressed by adding an MEK inhibitor, suggesting that combination therapy may also reduce skin toxicities associated with monotherapy.

A phase I/II, open-label, multicohort trial involving 247 patients with metastatic melanoma and V600 mutations was conducted to test the efficacy and safety of combination therapy.[22] In part C of the trial, patients were randomly assigned to dabrafenib plus trametinib or dabrafenib alone. Compared with monotherapy, combination therapy improved the response rate (76% vs 54%; *P*=.03) and progression-free survival (9.4 vs 5.8 months; HR, 0.39; 95% CI, 0.25–0.62; *P*<.001). The incidence of cutaneous squamous cell skin carcinoma was lower in the combination arm (7% vs 19%). However, combination therapy resulted in more frequent pyrexia (71% vs 26%), 5% of which was grade 3/4. Most fever episodes did not require dose reduction.

NCCN Recommendations

The NCCN Melanoma Panel added dabrafenib monotherapy and combination therapy with dabrafenib and trametinib as preferred systemic treatment options for advanced or metastatic melanoma (see ME-E 1 of 4, page 626; trametinib monotherapy was also added under the category of "Other Active Regimens." Dabrafenib and trametinib monotherapies are category 1 recommendations based on phase III trial data, whereas their combination is a category 2A option based on phase I/II results. However, pending higher level data, panelists pointed out the likelihood that combination therapy may be superior over targeted monotherapy. Two phase III clinical trials are underway to compare combination therapy with dabrafenib or vemurafenib monotherapy (ClinicalTrials.gov identifiers: NCT01584648 and NCT01597908). If the combination approach is confirmed to improve response, lower toxicity, and/or delay resistance, as suggested by the phase I/II trial, it may become the preferred choice over monotherapy with a BRAF inhibitor.

Like vemurafenib, dabrafenib and trametinib are only recommended for patients with documented V600 *BRAF* mutations. The panel preferred BRAF inhibition over trametinib monotherapy, and did not recommend trametinib monotherapy for patients who experienced disease progression after previous treatment with BRAF inhibitors. Trametinib monotherapy can be used in patients who are intolerant to toxicities associated with vemurafenib or dabrafenib.

Although dabrafenib is not associated with as much photosensitivity as vemurafenib, regular skin evaluation and referral to a dermatologist are still recommended, because secondary skin lesions, a class-like effect of BRAF inhibition, can develop. Fever is a toxicity specific to dabrafenib and should be managed with the use of antipyretics, such as acetaminophen and/or nonsteroidal anti-inflammatory drugs, and, if necessary, temporary discontinuation of therapy. Patients treated with dabrafenib should also be educated to report joint pain and swelling.

Conclusions

These NCCN Guidelines Insights highlight important updates to the management of melanoma in the NCCN Guidelines for Melanoma. 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, where available, combined with expert consensus of the NCCN 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 NCCN panel strongly encourages participation in prospective clinical trials.

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Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/45601;** and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.

Posttest Questions

1. Which of the following is false regarding adjuvant radiation for patients with high-risk resected melanoma?
   a. Adjuvant radiation is associated with lower nodal recurrence
   b. Adjuvant radiation is associated with improved relapse-free survival
   c. Adjuvant radiation is associated with frequent long-term toxicities
   d. None of the above
2. True or False: Chronic sun damage melanoma has a significantly higher proportion of *BRAF* mutations compared with nonchronic sun damage melanoma.
3. Which of the following is an NCCN preferred regimen for patients with advanced melanoma harboring a V600 mutation?
   a. Dabrafenib plus trametinib
   b. Dabrafenib monotherapy
   c. Trametinib monotherapy
   d. a and b
   e. a, b, and c