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Melanoma, Version 2.2016

Clinical Practice Guidelines in Oncology

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Abstract

This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma focuses on adjuvant therapy and treatment of in-transit disease, because substantial changes were made to the recommendations for the 2016 update. Depending on the stage of the disease, options for adjuvant therapy now include biochemotherapy and high-dose ipilimumab. Treatment options for in-transit disease now include intralesional injection with talimogene laherparepvec (T-VEC), a new immunotherapy. These additions prompted reassessment of the data supporting older recommended treatment options for adjuvant therapy and in-transit disease, resulting in extensive revisions to the supporting discussion sections.

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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 2016, an estimated 76,380 patients will be diagnosed with and approximately 10,130 patients will die of melanoma in the United States.[1] However, these figures for new cases may represent a substantial underestimate, as many superficial and in situ melanomas treated in the outpatient setting are not reported. The incidence of melanoma continues to increase dramatically, at an overall rate of 33% for men and 23% women from 2002 to 2006.[2] Melanoma is increasing in men more rapidly than any other malignancy, and in women more rapidly than any other malignancy except lung cancer.[3] Based

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. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Melanoma are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**

Disclosures for the NCCN Melanoma Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Melanoma Panel members can be found on page 473. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

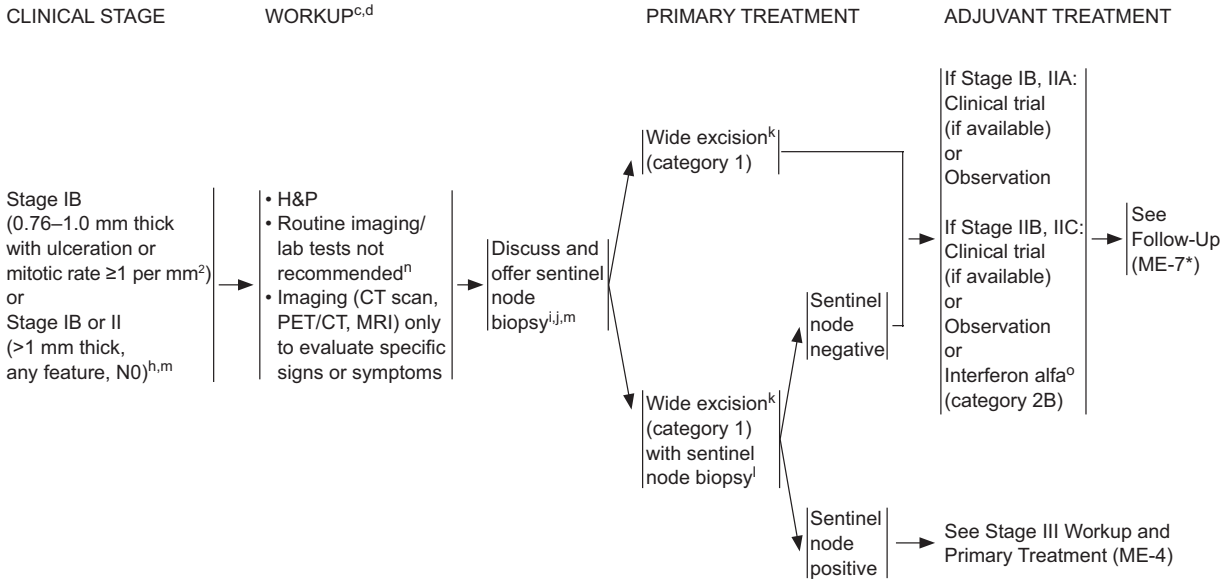
on data from 2009 to 2011, the lifetime risk of developing cutaneous melanoma is 1 in 34 for women and 1 in 53 for men. The median age at diagnosis is 59 years. On average, an individual loses 20.4 years of potential life as a result of melanoma mortality compared with 16.6 years for all malignancies.[4]

Risk factors for melanoma include skin type, personal history of prior melanoma, multiple clinically atypical moles or dysplastic nevi, a positive family history of melanoma,[5–8] and, rarely, inherited genetic mutations. Genetic counseling could be considered for individuals with a strong family history of invasive melanoma or pancreatic cancer. In addition to genetic factors, environmental factors including excess sun exposure and UV-based artificial tanning contribute to the development of melanoma.[9–11] The interaction between genetic susceptibility and environmental exposure is illustrated in individuals with an inability to tan and fair skin that sunburns easily; these individuals have a greater risk of developing melanoma.[12,13] However, melanoma can occur in any ethnic group and also in areas of the body without substantial sun exposure.

As with nearly all malignancies, the outcome of melanoma depends on the stage at presentation.[14] Experts estimate that, in the United States, 84% of patients with melanoma initially present with localized disease, 9% with regional disease, and 4% with distant metastatic disease.[15] In general, the prognosis is excellent for patients who present with localized disease and primary tumors 1.0 mm or less in thickness, with 5-year survival achieved in more than 90% of patients.[14] For patients with localized melanomas more than 1.0 mm in thickness, survival rates range from 50% to 90%, depending on tumor thickness, ulceration, and mitotic rate.[14]

Text cont. on page 458.

NCCN Melanoma Panel Members



*Available in the complete version of these guidelines at NCCN.org.

[h]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 to 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.

[m]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.

[c]While there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate benign from malignant neoplasms, or melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following SLNB) is not recommended outside of a clinical study (trial).

[d]In the absence of metastatic disease, *BRAF* testing of the primary melanoma is not recommended.

[i]Decision not to perform SLNB may be based on significant patient comorbidities, patient preference, or other factors.

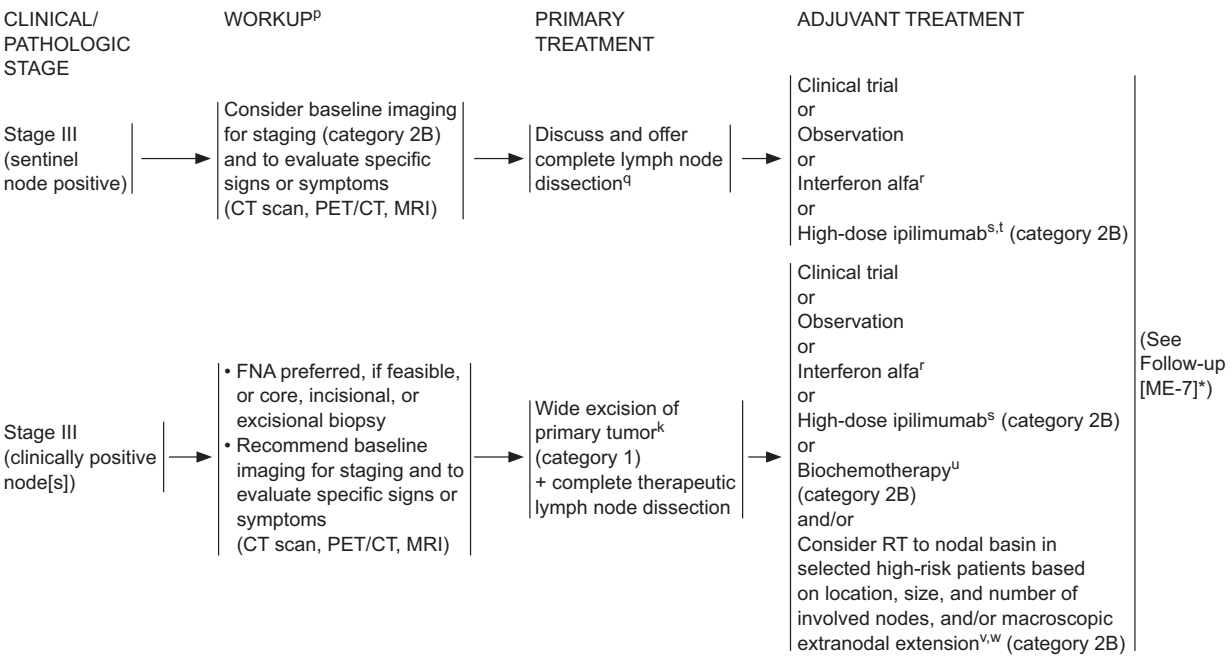
[j]SLNB is an important staging tool, but has not been shown to improve disease-specific survival among all patients. Subset analysis of prospectively collected data suggest that SLNB is associated with improvement in distant metastasis-free survival among patients with melanomas 1.2–3.5 mm thick, compared to patients with melanomas of similar thickness who are initially observed and subsequently develop clinical nodal metastases.

[k]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B)*.

[l]Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

[n]Consider nodal basin ultrasound prior to SLNB for melanoma patients with an equivocal regional lymph node physical exam. Nodal basin ultrasound is not a substitute for SLNB. Negative nodal basin ultrasound is not a substitute for biopsy of clinically suspicious lymph nodes. Abnormalities or suspicious lesions on nodal basin ultrasound should be confirmed histologically.

[o]High-dose alfa interferon for one year has been shown to improve disease-free survival (DFS) (category 1); its impact on overall survival remains unclear (category 2B)



*Available in the complete version of these guidelines at NCCN.org.

[k]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-B)*.

[p]Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but is not recommended for patients with cutaneous melanoma who are otherwise NED.

[q]CLND contributes to staging. Its impact on regional disease control and overall survival is the focus of ongoing clinical trials. Factors which predict non-sentinel lymph node positivity include sentinel node tumor burden, number of positive nodes, and thickness/ulceration of the primary tumor. See Principles of Complete Lymph Node Dissection (ME-C)*.

[r]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); but there is no impact on overall survival.

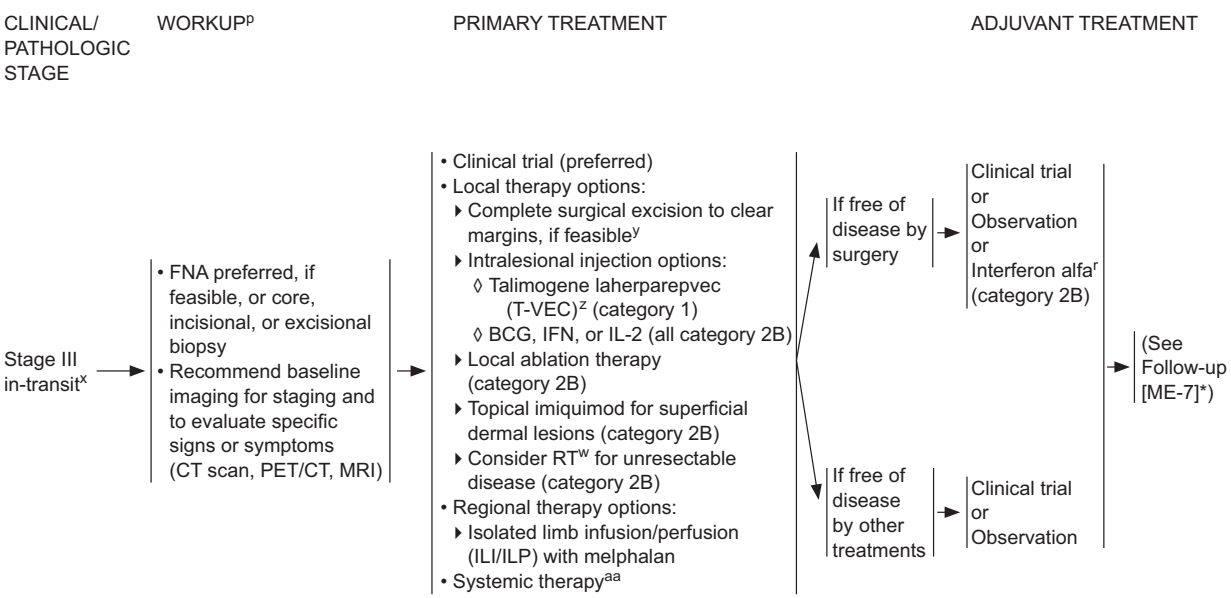
[s]Adjuvant ipilimumab is associated with improvement in recurrence-free survival. Its impact on overall survival has not been reported. The recommended dose of ipilimumab (10 mg/kg) was associated with adverse events which led to the discontinuation of treatment in 52% of patients. There was a 1% drug-related mortality rate.

[t]The clinical trial excluded patients with sentinel lymph node metastases ≤1 mm in size and who did not undergo CLND. The decision to use ipilimumab should be based on risk of recurrence balanced against the risk of treatment-related toxicity. It is unclear whether the decision should be based on CLND.

[u]For biochemotherapy, See Other Systemic Therapies (ME-E 2 of 6)*.

[v]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in relapse-free or overall survival. Its benefits must be weighed against potential toxicities.

[w]See Principles of Radiation Therapy for Melanoma (ME-D).



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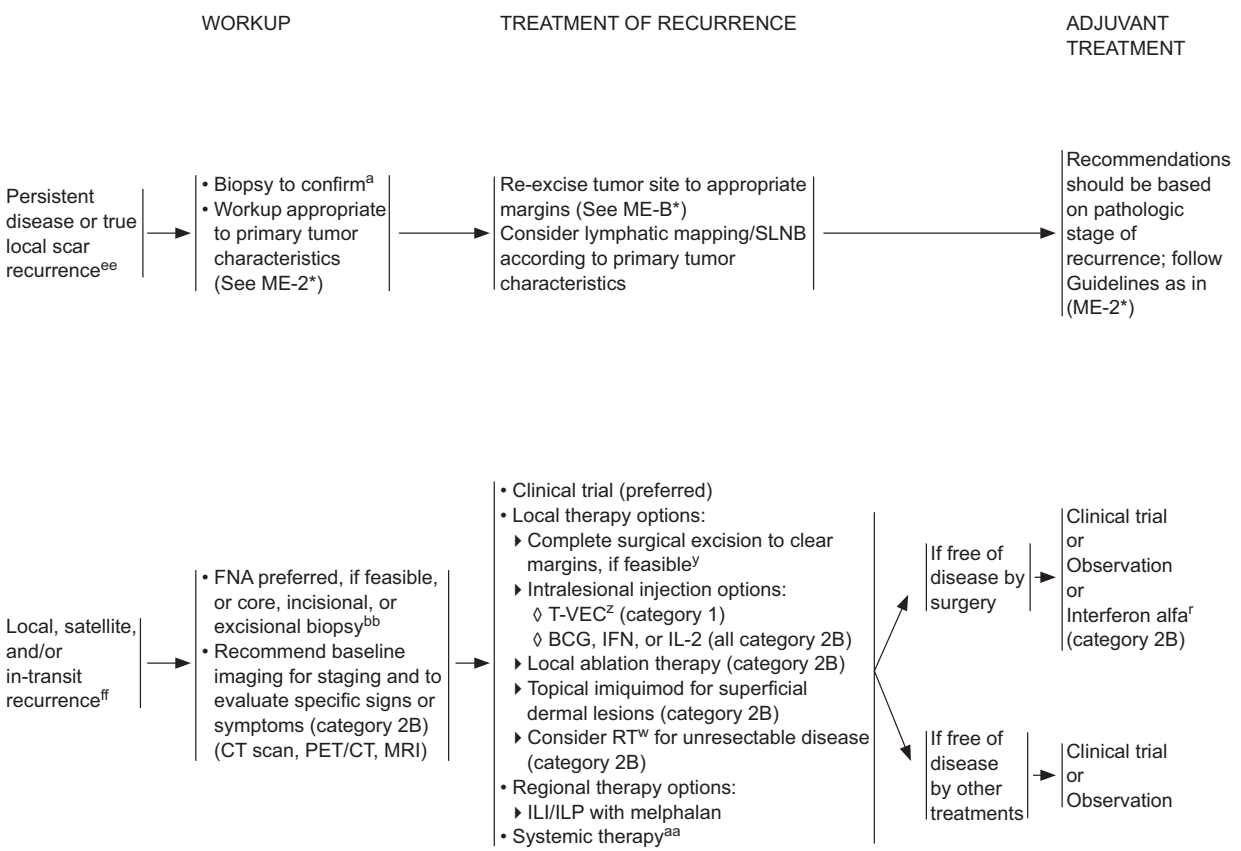
[w]See Principles of Radiation Therapy for Melanoma (ME-D).

[x]In-transit metastasis is defined as intralymphatic tumor in skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond the nearest regional lymph node basin. (Definition from CAP 2012 Melanoma Protocol [version 3.2.0.0])

[y]Consider sentinel node biopsy for resectable in-transit disease (category 2B). Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

[z]T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was noted in Stage IIIB, IIIC and Stage IV-M1a disease and was more likely in patients who were treatment naive.

[aa]See Systemic Therapy for Metastatic or Unresectable Disease (ME-E 1 of 6)*.



*Available in the complete version of these guidelines at NCCN.org.

[a]See Principles of Biopsy and Pathology (ME-A)*.

[r]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); but there is no impact on overall survival.

[w]See Principles of Radiation Therapy for Melanoma (ME-D).

[y]Consider sentinel node biopsy for resectable in-transit disease (category 2B). Sentinel lymph nodes should be evaluated with multiple sectioning and immunohistochemistry.

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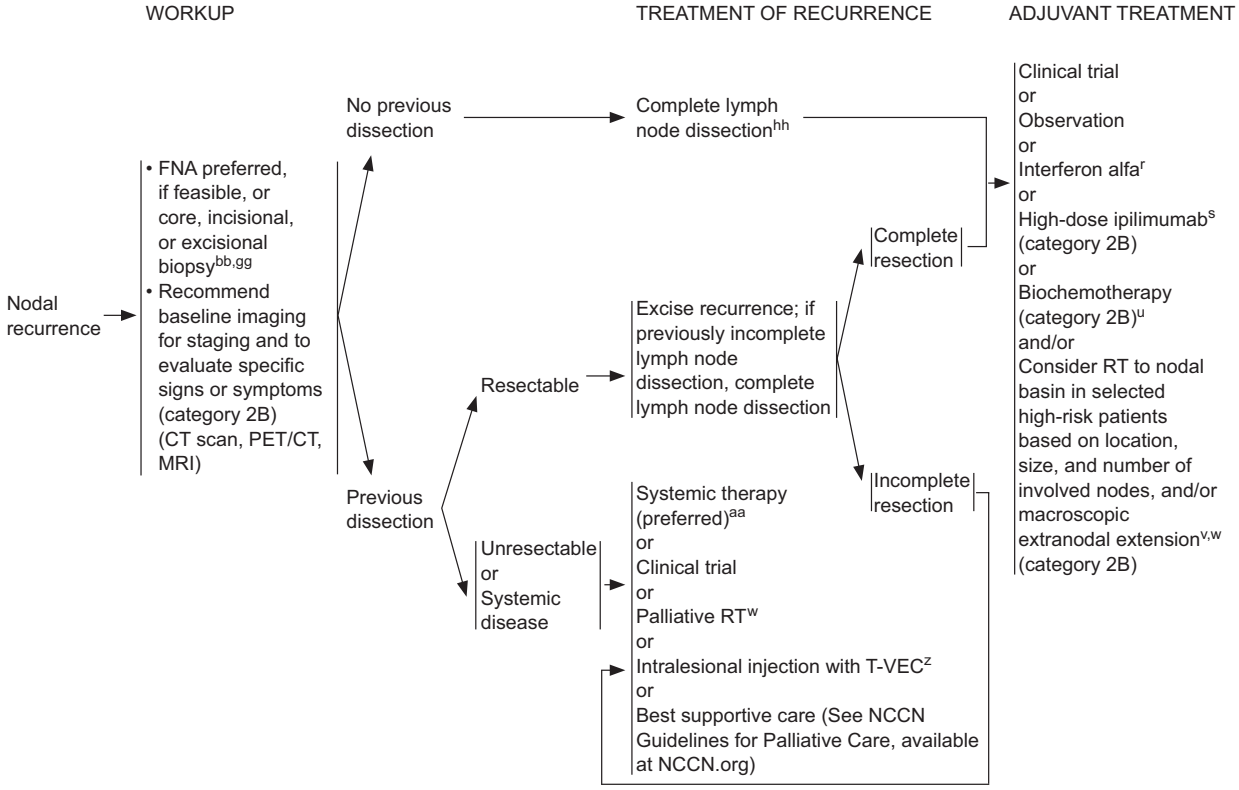
[aa]See Systemic Therapy for Metastatic or Unresectable Disease (ME-E 1 of 6)*.

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

[ee]Persistent disease or true local scar recurrence is defined by presence of in situ and/or radial growth phase.

[ff]Local, satellite recurrence without in situ or radial growth phase, with deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar.



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[u]For biochemotherapy, See Other Systemic Therapies (ME-E 2 of 6)*.

[v]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in relapse-free or overall survival, and its benefits must be weighed against potential toxicities.

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

[gg]Biopsy preferred if recurrence is unresectable.

[hh]See Principles of Complete Lymph Node Dissection (ME-C)*.

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Consider RT in the following situations:[1]

PRIMARY DISEASE

- Adjuvant treatment in selected patients with factors including, but not limited to deep desmoplastic melanoma with narrow margins, extensive neurotropism, or locally recurrent disease.

REGIONAL DISEASE [2]

- Adjuvant treatment in selected patients following resection of clinically appreciable nodes (category 2B)[3] if
  - Extranodal tumor 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, available at NCCN.org)
  - Stereotactic radiosurgery either as adjuvant or primary treatment
  - Whole brain radiation therapy, either as adjuvant (category 2B) or primary treatment[4]
- Other symptomatic or potentially symptomatic soft tissue and/or bone metastases[2]

[1]Interactions between radiation therapy and systemic therapies (eg, *BRAF* inhibitors, interferon alfa-2b, immunotherapies, checkpoint inhibitors) need to be very carefully considered as there is potential for increased toxicity.

[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 shown no improvement in relapse-free or overall survival. Its benefits must be weighed against potential toxicities.

[4]Adjuvant whole brain radiation following resected melanoma brain metastasis is controversial and should be considered on an individual patient basis.

ME-D
(1 OF 3)

Text cont. from page 451.

The likelihood of regional nodal involvement increases with increasing tumor thickness and the presence of ulceration and mitotic rate.[16–19] When regional nodes are involved, survival rates are roughly halved. However, within stage III, 5-year survival rates range from 20% to 70%, depending primarily on the nodal tumor burden.[14] Historically, long-term survival in patients with distant metastatic melanoma, taken as a whole, has been less than 10%. However, even within stage IV, some patients have a more indolent clinical course that is biologically distinct from that of most patients with advanced disease. Furthermore, the impact of emerging effective systemic therapies on the survival of patients with stage IV melanoma, either at presentation or recurrence, may make long-term remission possible for a larger proportion of patients.

With the advent of targeted therapy, there is increasing appreciation of the potential therapeutic implications of the variable incidence of specific genetic alterations among distinct clinical subtypes of melanoma. The currently described clinical subtypes of cutaneous melanoma are non-chronic sun damage (non-CSD), which are melanomas on skin without chronic sun-induced damage; CSD, which are melanomas on skin with chronic sun-induced damage signified by the presence of marked solar elastosis; and acral, which are melanomas on the soles, palms, or subungual sites. Melanocytes exist outside of the skin, as well, and can give rise to noncutaneous melanomas on mucosal membranes, the uveal tract of the eye, or leptomeninges.[20] In an analysis of 102 primary melanomas, the non-CSD subtype was found to have the highest proportion of *BRAF* mutations (56%) compared with CSD, acral, and mucosal subtypes (6%, 21%, and 3%, respectively).[21] Conversely, incidence of KIT aberrations was 28%, 36%, and 39% in CSD, acral, and mucosal subtypes, respectively, but 0% in non-CSD subtypes. NRAS mutations were found in 5% to 20% of the subtypes.

By definition, the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatment. Exceptions to general rules were discussed among the panel members while developing these guidelines. A 5% rule (omitting clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. The NCCN Panel on melanoma strongly supports early diagnosis and appropriate treatment of melanoma, including participation in clinical trials where available.

Mucosal and uveal melanoma differ significantly from cutaneous melanoma in presentation, genetic profile, staging, response to treatment, and patterns of progression.[22–24] Ideally, mucosal and uveal melanoma should be treated as diseases distinct from cutaneous melanoma, with care tailored to the individual. The NCCN Guidelines for Melanoma do not include recommendations for the diagnostic workup or treatment of early-stage mucosal or uveal melanoma. Guidelines for initial diagnostic workup and treatment of mucosal melanoma of the head and neck can be found in the NCCN Guidelines for Head and Neck Cancers (to view the most recent version, visit NCCN.org). For systemic therapy of stage IVB or IVC mucosal melanoma of the head or neck, however, the NCCN Guidelines for Head and Neck Cancers points to the NCCN Guidelines for Melanoma recommendations for systemic therapy for metastatic or unresectable disease. The NCCN Guidelines currently do not include recommendations for initial diagnosis and treatment of early-stage uveal melanoma or anogenital mucosal melanoma.

Adjuvant Systemic Therapy for Melanoma

For adjuvant treatment of melanoma in patients rendered free of disease by surgery, most traditional chemotherapy approaches have proven to be ineffective. Adjuvant interferon (IFN), particularly high-dose IFN, has been widely used in patients with melanoma, and as is described subsequently, a large body of clinical evidence has amassed. Results from recent and ongoing trials support 2 new types of adjuvant treatment for melanoma: (1) biochemotherapy, a combination of high-dose IFN, interleukin-2 (IL-2), and chemotherapy; and (2) immune checkpoint inhibitors.[25,26] Prospective clinical trials are evaluating targeted therapies and regimens combining multiple types of therapy (IFN, chemotherapy, immune checkpoint inhibitors, targeted therapies) for use as adjuvant treatment for melanoma.[27–42]

Low-Dose and Intermediate-Dose IFN

Low-dose adjuvant IFN typically has been administered subcutaneously at 3 MU per day for 3 days per

week. Various intervals and durations of low-dose IFN have been compared with observation in patients with fully resected nonmetastatic melanoma at high-risk for recurrence (Table 1). In these trials, patients with stage III in-transit disease were either explicitly excluded or very unlikely to have been included. Prospective randomized trials have shown that low-dose adjuvant IFN was not associated with statistically significant improvements in survival, and with a few notable exceptions, also did not provide statistically significant improvement in relapse-free survival (Table 1). Intermediate-dose IFN, defined as 5 to 10 MU per day subcutaneously for 3 to 5 days per week, has also been compared with observation as adjuvant therapy for resected, high-risk melanoma. As with low-dose IFN, prospective randomized studies showed that intermediate-dose adjuvant IFN did not improve survival, and results for relapse-free survival were inconsistent across trials (Table 1).

High-Dose IFN and Pegylated IFN

High-dose IFN generally includes 1 month of intravenous induction with 20 MU/m^2/d for 5 days per week followed by 11 months of intermediate-dose subcutaneous maintenance IFN with 10 MU/m^2/d for 3 days per week. This regimen has been evaluated in 5 large prospective randomized clinical trials in patients with fully resected nonmetastatic melanoma at high risk for recurrence (Table 2). The

Table 1. Studies Comparing Low-Dose or Intermediate-Dose Adjuvant Interferon with Observation

				Patients, n		Statistically Significant Impact of IFN	
Trial[a]	References	IFN Dose[b]	IFN Type	IFN	Obs	Relapse-free Survival[c]	Survival[d]
Italian Skin Cancer Foundation[e]	Rusciani et al,[43] 1997	Low	2B	84	70	Yes; *P*<.0001[f]	No
Austrian Malignant Melanoma Group	Pehamberger et al,[44] 1998	Low[g]	2a	143	150	Yes; *P*=.02	No
French Cooperative Group on Melanoma	Grob et al,[45] 1998	Low	2a	244	243	Yes; *P*=.035	Trend: *P*=.059
Scottish Melanoma Group Study	Cameron et al,[46] 2001	Low	2b	49	47	Overall: No 2-y rate: Yes; *P*<.05	No
WHO Melanoma Programme	Cascinelli et al,[47] 2001	Low	2a	225	219	No	No
AIM HIGH – UK Coordinating Committee on Cancer Research	Hancock et al,[48] 2004	Low	2a	338	336	No	No
EORTC 18871 and DKG-80-1	Kleeberg et al,[49] 2004	Very low	2b	240	244	No	No
ECOG 1690	Kirkwood et al,[50] 2000 Kirkwood et al,[51] 2004	Low	2b	215	212	No	No
EORTC 18952	Eggermont et al,[52] 2016	Intermediate	2b	1109	279	No[h]	No[h]
DeCOG trial	Garbe et al,[53] 2008	Low	2a	148	148	Yes; *P*=.018	Yes; *P*=.005
Nordic IFN trial	Hanssonet al,[54] 2011	Intermediate	2b	571	284	Yes; *P*=.034[i]	No

Abbreviations: IFN, interferon; NR, not reported; Obs, observation; SC, subcutaneously.
[a]All prospective, randomized, multicenter studies comparing adjuvant IFN with observation in patients with fully resected nonmetastatic cutaneus melanoma at high-risk for recurrence.
[b]Low-dose IFN regimen: 3 MU SC 3X/week, for various intervals and durations; very low dose IFN regimen: 1 MU SC every other day; intermediate-dose IFN regimens: 10 MU SC 3–5X/week for 4 weeks, then 5-10 MU SC 3X/week.
[c]Relapse-free survival, relapse-free interval, recurrence-free survival, disease-free survival, progression-free survival, or metastasis rate.
[d]Overall survival or melanoma-specific survival.
[e]Included only stage I and II.
[f]No significant improvement for patients with stage I or Breslow thickness <1.5 mm.
[g]IFN regimen: 3 MU SC daily for 3 weeks, then 3X/week.
[h]Subgroup analyses showed that the longer IFN regimen (25 months) was associated with statistically significant improvement (P<.001) in relapse-free survival, distant metastasis-free survival and overall survival for patients with ulcerated primary lesions.
[i]Exploratory subset analysis showed that largest effects were in patients with highest disease burden before resection (stage III, more involved lymph nodes), and nonulcerated primary tumor.

smallest of these trials, ECOG E2696, was the only one to specifically allow recruitment of patients with in-transit disease.

Results from these trials vary but nonetheless suggest that high-dose adjuvant IFN can provide statistically significant improvement in relapse-free survival and sometimes overall survival (OS), at least at early time-points. Both of these effects appear to diminish with longer-follow-up, however (Table 2). The variability of results suggests that clinical benefit from adjuvant high-dose IFN may be limited to a subset of patients, but it remains unclear which if any subsets of patients are most likely to benefit. Of note, ECOG 1690 showed that high-dose but not low-dose IFN significantly improved relapse-free survival compared with observation (Tables 1 and 2).[50]

In an attempt to reduce toxicities associated with adjuvant high-dose IFN, randomized trials have compared different dose schedules and durations.[55–60] Results differ across trials, however, so it is unclear which schedules, if any, provide greater clinical benefit than the standard regimen.

Pegylated IFN was also tested as an adjuvant therapy with potentially better risk–benefit profile. The EORTC 18991 phase III randomized trial compared pegylated IFN-alfa-2b with observation in 1256 patients with completely resected stage III melanoma (without distant or in-transit metastases). The pegylated IFN regimen included induction with 6 mcg/kg subcutaneously per week for 8 weeks followed by maintenance with 3 mcg/kg subcutaneously per week for an intended duration of 5 years.[61] Pegylated IFN improved recurrence-free survival compared with observation (4-year recurrence-free survival, 45.6% vs 38.9%; *P*=.01); however, no statistically significant effect was seen on OS. Based on these data, pegylated IFN-alfa received approval by the United States FDA in 2011 as an adjuvant therapy option for patients with melanoma involving regional lymph nodes. After extended follow-up, however, the effect on recurrence-free survival had only borderline statistical significance (7-year recurrence-free survival, 39.1% vs 34.6%; hazard ratio [HR], 0.87; 95% CI, 0.76–1.00; *P*=.055).[62] No statistically significant effects were seen on distant metastases-free survival and OS. Subset analysis showed that patients more likely to benefit from pegylated IFN were those with microscopic nodal metastasis (not clinically palpable) either limited to 1 node or associated with an ulcerated primary lesion.

Biochemotherapy

For patients with completely resected high-risk stage III disease, biochemotherapy may be an appropriate adjuvant treatment option. Biochemotherapy may be generally defined as any regimen that includes

Table 2. Studies of High-Dose Interferon in Nonmetastatic Melanoma[a]

			Patients, n		Median Follow-up	Statistically Significant Impact of IFN	
Trial[b]	References	IFN Type	IFN	Obs		Relapse-Free Survival[c]	Survival[d]
ECOG 1684	Kirkwood et al,[63] 1996	2b	143	137	6.9 y	Yes; *P*=.0023	Yes; *P*=.0237
	Kirkwood et al,[51] 2004				12.6 y	Yes; *P*=.02	No
ECOG 1690	Kirkwood et al,[50] 2000	2b	215	212	4.3 y	Yes; *P*=.05	No
	Kirkwood et al,[51] 2004				6.6 y	Trend; *P*=.09	No
ECOG 1694	Kirkwood et al,[64] 2001	2b	440	440[e]	1.3 y	Yes; *P*=.0027	Yes; *P*=.0147
	Kirkwood et al,[51] 2004				2.1 y	Yes; *P*=.006	Yes; *P*=.04
ECOG E2696	Kirkwood et al,[64] 2001	2b	72[f]	35[f]	1.9 y	Yes; *P*=.03	No
	Kirkwood et al,[51] 2004				2.8 y	No	No
Sunbelt trial	McMasters et al,[65] 2016	2b	112	106	5.9 y	No	No

Abbreviations: IFN, interferon; IV, intravenously, NR, not reported; Obs, observation; SC, subcutaneously..
[a]High-dose IFN regimen: 20 MU/m^2/d IV for 5 d/wk for 4 weeks, then 10 MU/m^2/d SC for 3 d/wk for 48 weeks.
[b]All prospective, randomized, multicenter studies comparing adjuvant interferon with observation in patients with fully resected cutaneus non-metastatic melanoma at high risk for recurrence.
[c]Relapse-free survival for ECOG trials; disease-free survival for Sunbelt Trial.
[d]Overall survival or melanoma-specific survival.
[e]Control was GM2-KLH21 vaccine (GMK) instead of observation.
[f]Treatment arms: A, GMK + high-dose IFN alfa-2b (n=36); B: GMK alone; then GMK + high-dose IFN alfa-2b (n=36); C: GMK alone (n=35); *P*=.03 for relapse-free survival from B versus C using Cox regression analysis.

both chemotherapy and immunotherapy, usually IFN and/or IL-2. Adjuvant biochemotherapy with cisplatin, vinblastine, dacarbazine, IL-2, and IFN was compared with high-dose IFN alfa-2b monotherapy in the SWOG S0008 phase 3 randomized trial.[25] Eligible patients had fully resected stage III cutaneous melanoma, including all except for the lowest risk substage, stage IIIA–N1a (nonulcerated primary tumor with micrometastasis in 1 sentinel lymph node). Patients were more likely to complete the 9-week biochemotherapy course versus the 52-week course of IFN-alfa-2b (80% vs 43% completion rate; $P<.001$). After a median follow-up of 7.2 years, patients treated with biochemotherapy showed improved median recurrence-free survival of 4.0 years compared with 1.9 years for high-dose IFN alfa-2b (HR, 0.75; 95% CI, 0.58–0.97; $P=.03$). Median and 5-year OS rates were not significantly different between the 2 treatment groups. Although the overall percentage of patients who experienced grade 3 to 5 adverse events was similar between treatment arms (76% for biochemotherapy vs 64% for IFN-alfa-2a), the toxicity profiles for each regimen were different. IFN-alfa-2a was associated with significantly higher rates of liver enzyme elevations, and biochemotherapy was associated with significantly higher rates of hypotension and hematologic, gastrointestinal, and metabolic toxicities.

High-Dose Ipilimumab

Immune checkpoint inhibitors, a relatively new class of therapies, target molecules involved in T-cell activation to promote immune responses needed to fight cancer. Ipilimumab, a monoclonal antibody directed to the immune checkpoint receptor CTLA-4, has been shown to significantly improve progression-free survival and OS in patients with unresectable or metastatic melanoma, and originally received FDA approval in 2011 for treatment of patients with metastatic melanoma. Based on its efficacy for treating metastatic disease, researchers performed a phase 3 double-blind, randomized multicenter international trial (EORTC 18071) comparing adjuvant high-dose ipilimumab (10 mg/kg) to placebo in patients with completely resected stage III melanoma. Eligible patients included those with stage IIIA disease (if N1a, at least one metastasis >1 mm), or with stage IIIB-C disease but no in-transit metastases.

All patients underwent primary tumor excision with adequate margins and complete regional lymphadenectomy, but no patients had received systemic therapy for melanoma.[26] The trial demonstrated improved recurrence-free survival: median 26.1 months with ipilimumab versus 17.1 months with placebo (HR stratified by stage, 0.75; $P=.0013$).[26,66] Based on these results, the FDA approved high-dose ipilimumab for adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes greater than 1 mm in diameter who have undergone complete resection, including total lymphadenectomy.[66] The approved indication mostly mirrors the trial inclusion criteria, but also includes patients with stage III in-transit disease and those who had received prior systemic therapy for melanoma.[26,66]

Adjuvant ipilimumab was tested and FDA approved with a prolonged high-dose regimen: 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity.[26,66] In contrast, for treatment of unresectable or metastatic disease, the recommended ipilimumab dose is much lower (3 mg/kg) and the treatment duration is much shorter (every 3 weeks for a total of 4 doses).[66] Ipilimumab is associated with a variety of immune-related adverse events, and the frequency and severity of these toxicities has been shown to increase with dose.[67–70] A meta-analysis including 1265 patients from 22 clinical trials found that the risk of developing an immune-related adverse event (any grade) was threefold higher with ipilimumab 10 mg/kg versus 3 mg/kg.[68]

In EORTC 18071, grade 3 to 4 adverse events were more common with ipilimumab versus placebo (54% vs 25%), as were immune-related adverse events (grade 3, 37% vs 2%; grade 4, 6% vs <1%).[26] Fatal ipilimumab-related adverse events occurred in 5 patients (1%), and included colitis with gastrointestinal perforation (n=3), myocarditis (n=1), and multiorgan failure with Guillain-Barre syndrome (n=1).

NCCN Recommendations

For patients with node-negative, early-stage melanoma who are at risk for recurrence (stage IB or stage II, ≤1.0 mm thick with ulceration or mitotic rate ≥1 per mm^2, or >1.0 mm thick), postoperative management options include participation in a clinical trial or observation. For patients with node-negative stage IIB or IIC disease, postoperative treatment options

include participation in a clinical trial, observation, or high-dose IFN alfa (category 2B).

For all patients with stage III melanoma, postoperative management options include participation in a clinical trial and observation. For those with completely resected stage III melanoma, additional postoperative management options may include high-dose or pegylated IFN, biochemotherapy, or high-dose ipilimumab. Selection of an active adjuvant treatment for these patients depends on many factors, including patient preference, patient age and comorbidities, and risk of recurrence.

Interferon: Due to the inconsistency of results, NCCN does not recommend use of low-dose or intermediate-dose IFN.

Adjuvant high-dose and pegylated IFN are both appropriate options for patients with completely resected stage III disease. This recommendation is category 2A for patients with either positive sentinel nodes or clinically positive nodes. There is panel consensus that high-level evidence supports IFN therapy for improving relapse-free survival in these patients, but that the effect of IFN on OS did not achieve statistical significance with long-term follow-up. Adjuvant high-dose IFN is a potentially toxic therapy that is not being used in all institutions, but panelists agree that it still may have a role in certain settings. The clinical trials cited previously included very few patients with in-transit disease. Hence adjuvant IFN is a category 2B recommendation for patients with completely resected stage III in-transit disease. Decisions about adjuvant IFN treatment should be made on an individual basis, after a thorough discussion with the patient about the potential benefits and side effects of therapy. If the decision is made to use adjuvant IFN, the best available evidence suggests that options include using either high-dose IFN with a planned duration of up to a year, or pegylated IFN with a planned duration of up to 5 years.

High-Dose Ipilimumab: Based on results of EORTC 18071, adjuvant high-dose ipilimumab is included as an adjuvant treatment option for select patients. NCCN acknowledges high-dose ipilimumab monotherapy as an adjuvant treatment option for resected (1) stage IIIA with metastases greater than 1 mm; (2) stage IIIB-C; or (3) nodal recurrence. Enthusiasm for this approach is tempered by the high rates of severe toxicities associated with the recommended adjuvant dose and duration of treatment. The decision to recommend a course of adjuvant ipilimumab should be informed by careful consideration of a patient's individual risk recurrence and their ability to tolerate and manage toxicities. The subset of patients with stage IIIA disease in this trial was small; the benefit of high-dose adjuvant ipilimumab in this particular subset is less well defined. Completion lymph node dissection (CLND) was required for ipilimumab treatment in the trial; however, it is not clear that patients opting out of CLND should necessarily be excluded from consideration for this option, as ipilimumab has demonstrated efficacy in treating metastatic disease, including nodal metastases.

Biochemotherapy: Based on the results of SWOG S0008, biochemotherapy is another adjuvant option for patients with completely resected stage III disease. Although the trial included some patients with stage III sentinel node positive disease and patients with stage III in-transit disease, the panel voted against including biochemotherapy as an adjuvant treatment option for these pathways based the toxicity and limited benefit restricted to recurrence-free survival but not OS.

Adjuvant Radiation Therapy

Adjuvant Radiation for Desmoplastic Neurotropic Melanoma

Adjuvant radiation therapy (RT) is rarely necessary after adequate excision of a primary melanoma. One exception may be desmoplastic neurotropic melanoma (DNM), which tends to be locally aggressive. In a retrospective series of 128 patients with DNM (84% stage II), patients who did and did not receive adjuvant radiation had a similar incidence of local failure (7% with RT vs 6% without) despite worse prognostic features in the radiated group (thicker tumors, deeper Clark level invasion, and narrower excision margins).[71] The authors concluded that RT should be considered for patients with inadequate margins, which in this series occurred predominately in the head and neck region.

A multicenter retrospective analysis in 277 patients with primary stage I–III desmoplastic melanoma treated with wide excision with or without sentinel lymph node biopsy (SLNB) showed that adjuvant RT was associated with improved local control, particularly in patients with positive excision margins

or primary melanoma with Breslow thickness greater than 4 mm or located in the head and neck region.[72] Another retrospective study of patients with resected recurrent desmoplastic melanoma (n=130) also showed that adjuvant RT was associated with improved local control but not distant metastasis-free survival.[73] The association of RT with improved local control was particularly evident in those with pure desmoplastic melanoma or those with perineural invasion. The utility of RT for local control of desmoplastic melanoma is further supported by the results from another single-institution retrospective analysis (n=95) showing a trend toward improved relapse-free survival in patients who received RT in addition to surgery.[74] Results from these 4 and 1 smaller retrospective study[75] suggest that adjuvant radiation therapy improves local control in patients with desmoplastic melanoma. This hypothesis is being tested in an ongoing phase III trial comparing adjuvant RT with observation after resection of neurotropic melanoma of the head and neck (Clinicaltrials.gov identifier: NCT00975520).[76]

Adjuvant Radiation for Preventing Nodal Relapse

Radiation has a role in controlling nodal relapse in patients at risk. The largest retrospective review investigating the role of RT was performed by Agrawal et al.[77] Based on lymph node number, size, location, and extracapsular extension, 615 patients met the specific criteria portending a "high risk" of regional nodal relapse. At a median follow-up of 5 years, regional recurrence occurred in only 10% of the patients selected to receive adjuvant RT, compared with 41% of the patients who did not receive RT. Adjuvant radiation was associated with improved locoregional control on multivariate analysis ($P<.0001$). Of note, treatment-related morbidity was significantly increased with RT (5-year rate, 20% vs 13%; $P=.004$), particularly lymphedema. Subsequent smaller retrospective analyses have also shown that adjuvant RT after surgery is associated with improved nodal basin control in patients with who are at high risk of regional recurrence.[78,79] One retrospective analysis suggested that the benefit of RT for regional control may be associated with doses of at least 50 Gy.[80] Interpretation of these results should take into consideration selection bias and other potential forms of bias inherent in retrospective studies.

The only prospective randomized phase III trial of adjuvant nodal basin RT versus observation in patients at risk for nodal relapses recently reported final results. This trial included 250 patients with non-metastatic disease and palpable lymphadenopathy at diagnosis or as an isolated palpable site of relapse.[81] Eligible patients were required to have an L-lactate dehydrogenase less than 1.5 times the upper limit of normal, as well as 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 neck, 4 cm or greater in the axilla or groin, or nodal extracapsular extension.[82] Patients were treated with lymphadenectomy followed by either adjuvant radiation (48 Gy in 20 fractions) to the nodal basin or observation.[81] After a mean of follow-up of 73 months, lymph node field recurrence was significantly less frequent in the adjuvant radiation group (HR, 0.54; 95% CI, 0.33–0.89; $P=.021$) for all nodal basins.[81] Although not primary endpoints, relapse-free survival and OS showed no statistically significant differences for patients treated with adjuvant RT versus observation. Adjuvant radiation was associated with frequent grade 2 to 4 toxicities primarily affecting the skin or subcutaneous tissue, but also including pain, nerve damage, and joint adverse events.

Various fractionation schemes for postoperative adjuvant radiation have been evaluated in retrospective studies.[72,83–87] Hypofractionated radiotherapy appears to be equally effective as standard fractionation. These studies have shown moderate toxicity associated with adjuvant RT. Although some doses/schedules may be better tolerated, prospective analyses are needed to establish the optimal regimen.

Adjuvant Radiation for Brain Metastases

Adjuvant radiation is also used after surgery for melanoma brain metastases. Prospective randomized trials have compared adjuvant whole-brain radiation therapy (WBRT) with observation, given after surgery or stereotactic radiosurgery (SRS) in patients with brain metastases from various types of cancer.[88–94] All but one of these studies showed that adjuvant WBRT reduces intracranial recurrence, and some studies also show improved duration of functional independence and reduced mortality due to intracranial progression and neurologic causes. These trials included very few patients with melanoma, however, probably less than 60 patients in total, and did not report results specifically from patients with melanoma. The largest of these pro-

spective randomized trials included 18 patients with melanoma. It showed that adjuvant WBRT after resection or SRS reduced intracranial progression but did not lead to statistically significant improvements in OS or duration of functional independence.[94] A few retrospective studies have reported outcomes for patients with brain metastases from melanoma treated with adjuvant WBRT after either surgery or SRS, but data from these analyses are insufficient for evaluating the clinical value of adjuvant WBRT for patients with melanoma.[95,96] Further study in a prospective randomized trial setting is needed to assess the impact of WBRT on melanoma brain metastases, especially in the context of emerging data supporting the use of systemic therapy in patients with melanoma brain metastases.

No good prospective randomized trials testing adjuvant SRS after surgery for patients with brain metastases from melanoma are available. However, SRS is being increasingly used in an effort to reduce the risk of neurocognitive toxicities associated with WBRT.

NCCN Recommendations

Most patients with in situ or early-stage melanoma will be cured using primary excision alone. However, patients with desmoplastic melanomas, especially those with extensive neurotropism, are at high risk for local recurrence, especially if margins are suboptimal. Adjuvant radiation after surgery may be considered to improve local control.

Adjuvant RT may be considered for select patients with clinically positive nodes and features predicting a high risk of nodal basin relapse. The NCCN panel discussed at length the value of adjuvant RT in patients at high risk of recurrence. Panelists agreed that high-level evidence indicates that adjuvant RT is useful in delaying or preventing nodal relapse. However, some institutions argued that the increased incidence of late RT-related toxicity could potentially outweigh the benefit of reducing nodal basin recurrence. This, coupled with the statistically insignificant trend towards worse overall survival in the RT arm resulted in substantial heterogeneity of opinion among panel members as to the role of adjuvant nodal basin RT. Patient characteristics that suggest potential use of radiation are those used as entry criteria in the phase III trial described previously.[82] The use of adjuvant RT for these patients is a category 2B recommendation, reflecting nonuniform panel consensus on its value. Careful patient selection based on location, size, number of positive nodes, and gross (instead of histologic) extranodal extension is critical. 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. Consideration should be given to potential interactions between radiation and systemic therapy.

The current data regarding adjuvant RT, either WBRT or SRS, for resected brain metastases are insufficient to formulate a specific recommendation. Adjuvant RT should be considered for these patients on a case-by-case basis. With the advent of more effective systemic therapy, melanoma patients are living longer than in the past, and may be more susceptible to the long-term neurocognitive toxicity of WBRT. For adjuvant therapy of recurrent disease, see "Treatment of Recurrence" (page 455).

Treatment for Stage III In-transit Disease

The tumor burden, time course of appearance, and duration of in-transit disease is variable. In some patients, in-transit lesions remain confined to a region of the body for many years. This may occur in isolation or in combination with other sites of metastatic disease. A major concern in patients in which in-transit disease occurs in isolation is the high probability of subsequent development of visceral metastasis. Therapies for isolated in-transit disease can be organized as:

- Local therapy: local treatments reduce the morbidity of in transit lesions but have a low/variable effect on the appearance of new lesions.
- Regional therapy: regional therapies treat the entire lymphatic basin and may not only eliminate visible tumors but also prevent outgrowth of new lesions in the region.
- Systemic therapy: systemic treatments have antitumor effects on existing in-transit lesions and may help delay or prevent further regional or subsequent systemic recurrence.

Many different treatment options, mostly locoregional, are available to patients presenting with stage III in-transit metastases. The choice of therapy depends on the patient's health status, tumor burden, and size, location, and number of tumor deposits. Because the tempo of spread of in-transit disease is not always known at presentation, it may be reasonable to start with conservative local therapies and move to regional or systemic therapy if response to local therapy is short-lived.

Local Therapy

Excision to clear margins is the mainstay of treatment for limited resectable in-transit metastasis. Although in-transit disease has a high probability of clinically occult regional nodal involvement and a positive sentinel node in the presence of in-transit metastasis portends a more ominous prognosis, the impact of SLNB on outcome remains unknown.[97]

For patients for whom resection is not feasible, previous resections have been unsuccessful, or who refuse surgery, nonsurgical local approaches for treating stage III in-transit melanoma include intralesional injections, local ablation therapy, topical imiquimod, and RT.

Intralesional Injections: A variety of agents have been tested as intralesional injections for melanoma. Key results from those showing the most promise are summarized in Table 3.

Talimogene Laherparepvec (T-VEC): Intralesional or perilesional injection of melanoma metastases with granulocyte-macrophage colony-stimulating factor (GM-CSF) has shown modest response rates or stable disease in several small clinical studies.[98–101] These studies and others led to the development of T-VEC, an agent that uses a modified herpes simplex virus to induce tumor cell lysis and to deliver localized expression of GM-CSF to injected lesions.[102] A recent phase 3 trial in select patients with unresectable stage IIIB–IV melanoma randomized subjects to intralesional injection of T-VEC versus subcutaneous injection of GM-CSF.[103] Patients were required to have at least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions greater than 10 mm in diameter, bidimensionally measurable disease, and limited distant metastatic disease (with specific definitions). T-VEC produced clinically significant durable response rates in injected tumors and a bystander effect on some uninjected nonvisceral and visceral tumors (Table 3).[104] At a median follow-up of 44 months (range, 32–59 months), patients treated with T-VEC compared with GM-CSF showed a higher durable response rate (DRR, 16.3% vs 2.1%; $P<.001$) and overall response rate (26.4% vs 5.7%; $P<.001$; complete response in 11% vs <1%).[103]

Exploratory subset analyses showed that the effect of T-VEC on response was greater for patients with less advanced disease. Patients with stage IIIB or IIIC disease had a DRR of 33% with T-VEC compared with 0% for GM-CSF. For patients with stage IV–M1a disease, the effect of T-VEC on DRR was smaller (16.0% vs 2.3%). For patients with stage IV–M1b or M1c disease, however, the effects of T-VEC on DRR and OS were small and not statistically significant. The effect of T-VEC on DRR was far more profound in patients with previously untreated metastatic disease (23.9% vs 0%) than for those with previously treated metastatic disease (9.6% vs 5.6%).

Table 3. Agents Tested for Intralesional Injection

		Response Rates	
Injection Agent	**Key Published Clinical Studies**	**Injected Lesions**	**Uninjected Lesions**
Talimogene laherparepvec	Phase III trial[103,104]	≥50% decrease in size: 64%	≥50% decrease in size: 32% of non-visceral 15% of visceral
Interleukin-2	>5 non-comparative studies, including several phase II trials[105,106] and retrospective/observational analyses[116–119] 2014 systematic reviews and meta-analysis[107]	CR: 67%–96% 80% for dermal 73% for subcutaneous	No responses seen in 2 phase II trials
Bacillus Calmette-Guérin	>10 prospective pilot/retrospective studies[a] 1 prospective randomized study[112]	CR: 90% for dermal 45% for subcutaneous	Occasional responses observed
Rose Bengal	Phase I trial[114] Phase II trial[115]	OR: 46%–58%	OR: 27%

Abbreviations: CR, complete response, defined as the percent of lesions that disappeared; NR, not reported; OR, objective response, defined as the percent of lesions showing partial or complete response.
[a]Most included fewer than 30 patients. See Krown et al. 1978,[111] Morton et al.1974,[120] and Table 5 in Tan et al. 1993,[110] a pooled analysis of 15 studies.

For T-VEC, common toxicities (treatment-emergent in ≥20%, any grade) were fatigue, chills, pyrexia, nausea, flu-like illness, injection-site pain, and vomiting.[103] Treatment-related toxicities of grade 3 to 4 occurred in 11% of patients and included injection site reactions (eg, cellulitis, pain, peripheral edema), and systemic toxicities (fatigue, vomiting, and other flu-like symptoms).

Interleukin-2: Intralesional injection with IL-2 is supported by a number of clinical studies (Table 3). The complete response rate in IL-2 injected lesions may be as high as 70%. Although response rates are higher in cutaneous lesions, good response rates have been observed in subcutaneous lesions as well.[105] Intralesional injection of IL-2 is far less toxic than high-dose intravenous IL-2. Grade 1 to 2 adverse effects are common but manageable, and grade 3 to 4 toxicities are extremely rare.[105–107] Intralesional IL-2 is usually associated with an injection site inflammatory reaction, with local swelling, erythema, pain, and sometimes necrosis. Common systemic effects include fever and other flu-like symptoms (chills, fatigue, nausea, and emesis, sometimes stomach pain, diarrhea, and headache) that are usually mild and often respond to analgesics.[105,106,108]

Less Common Intralesional Injection Agents: IFN has been used as an intralesional injection agent for treating in-transit melanoma, although there is very little published evidence to support this approach (case reports and one small retrospective study[109]).

Intralesional bacillus Calmette-Guérin (BCG) has been shown to provide at least transient complete or partial responses in most injected lesions, with much higher response rates in cutaneous versus subcutaneous metastases (Table 3).[110–112] Although initial response rates are high for injected lesions, intralesional BCG is associated with a number of significant local and occasional systemic adverse effects.[111–113] BCG injection has been largely supplanted by other local injection options and is rarely used in clinical practice.

Rose bengal, a photosensitizing dye, is an investigational agent in development as another method for chemoablation of melanoma metastases by intralesional injection (using PV-10, a 10% w/v rose bengal saline solution).[114,115] It has similar activity to other intralesional agents, but is not currently available outside of the clinical trial setting (Clinicaltrials.gov indentifier: NCT02288897).

Other Local Therapies: *Local Ablation:* The efficacy of laser ablation, primarily carbon dioxide laser ablation, for treatment of melanoma metastases, is reported in a number of noncomparative retrospective analyses (15-100 patients/study).[121–127] Ablation can be effectively achieved with minimal toxicity,[121,123,124,127] but this technique has largely been supplanted by more contemporary approaches.

Topical Therapy: In patients with in-transit or locally metastatic disease, case reports suggest that imiquimod monotherapy can provide partial and complete responses in patients with cutaneous metastases, but it is less likely to be effective on deep dermal or subcutaneous metastases.[128–132] Other studies have shown that imiquimod used in combination with another local therapy can provide high rates of durable response in patients with locally metastatic melanoma.[130,133–139]

Topical immunotherapy using diphencyprone (DPCP), also known as diphenylcyclopropenone, has been studied in patients with in-transit melanoma, either alone or in combination with other concomitant therapies. As with topical imiquimod, supporting evidence for this approach comes primarily from case studies reporting remarkable responses in some patients.[140–147] One retrospective study included 50 patients with in-transit cutaneously metastatic melanoma treated for at least 1 month with DPCP.[148] Complete clearance of cutaneous disease was observed in 46% of patients, and another 38% showed partial response. DPCP is not FDA approved for this indication but may be available in the context of clinical trials.

RT: RT may be used for selected patients with unresectable symptomatic regional recurrences for whom there are no better options. A wide variety of dose schedules has been employed. (See "Palliative Radiation Therapy," available in the complete version of these guidelines at NCCN.org.).

Regional Therapy: Isolated Limb Perfusion and Infusion

For patients with regionally recurrent melanoma not suitable for local or topical therapy, regional administration of cytotoxic chemotherapy with either isolated limb perfusion (ILP) or isolated limb infusion (ILI) is designed to administer high doses to an affected extremity while avoiding toxicities associated with systemic

drug exposure. These approaches also allow delivery of chemotherapy under hyperthermic conditions, suggested by some studies to improve efficacy of cytotoxic agents,[149–154] but also associated with increased toxicity.[155,156] These approaches are limited to patients with regional metastases confined to an extremity.

ILP, the first of these techniques to be developed, was introduced in the late 1950s and has been refined and modified to improve response rates and minimize toxicities.[157,158] Although other agents have been used for ILP, and many have yet to be tested, melphalan (L-phenylalanine mustard) is the cytotoxic agent most commonly used, often in combination with either actinomycin D or TNF-alfa.[158–161] Response rates after ILP have improved as the method has been refined. A large systematic review (n=2018 ILPs; 22 trials) found that for patients with unresectable stage IIIB-IIIC metastatic melanoma of the limbs, studies published between 1990 and 2008 reported a median overall response rate of 90% (range, 64%–100%) and a median complete response rate of 58% (range, 25%–89%).[160] Median complete response rate varied somewhat depending on the agents used, ranging from 47% with single-agent melphalan, 45% to 65% for melphalan/actinomycin D combination, and up to 70% with melphalan/TNF-alfa combination.[160] These response rates are mostly derived from retrospective series, and the differences reported depend on definitions of response often spanning decades and on patient selection factors. The reported differences in response rates may not be clinically significant. For example, a prospective randomized clinical trial directly comparing hyperthermic ILP with single-agent melphalan to combination melphalan and TNF-alfa did not show a significant difference in response rate.[162] TNF-alfa is currently unavailable for use in the United States.

Disadvantages to ILP include the technical complexity and invasiveness of the procedure, which make it challenging (or contraindicated) in elderly and frail patients, and difficult to use again in the same patient in the event of recurrence or progression.[163] This approach should only be performed in centers with the expertise to manage both the procedure and the potential complications.

In the 1990s ILI was developed as a simpler and less invasive approach,[164] amenable to repeated applications,[165] and safe for use in elderly patients.[166] Melphalan is commonly used for ILI, often with actinomycin D.[167] The addition of papaverine for cutaneous vasodilation has been shown to increase response rate but also the risk of regional toxicity.[168,169] ILI is associated with lower rates of toxicity and morbidity compared with ILP, but retrospective comparisons of response and survival with ILP versus ILI have shown varying results.[168,170–174] An analysis of 7 studies involving 576 patients, primarily with stage III disease and treated with melphalan/actinomycin D combination via ILI, showed an overall response rate of 73%, with complete response in 33% (range, 26%–44% across studies), partial response in 40% (33%–53%), and stable disease in 14%.[167] A smaller pooled analysis of 2 additional studies (N=58), one a noncomparative phase II study (ClinicalTrials.gov identifier: NCT00004250), showed similar overall response rates for stage IIIB versus stage IIIC disease (48% vs 40%), and similar 5-year survival rates (38% vs 52%).[175] Complete responses were achieved in 25% of patients, partial responses in 20%.

NCCN Recommendations

Treatment in the context of a clinical trial is the preferred option for in-transit disease. For those with a single or a small number of resectable in-transit metastases, complete surgical excision with histologically negative margins is preferred, if feasible. In the patient undergoing curative resection of a solitary in-transit metastasis, SLNB can be considered (category 2B).

If complete surgical excision to clear margins is not feasible, treatment in the context of a clinical trial is generally the preferred option. Other local, regional, or systemic therapies can be considered. If the patient has a limited number of in-transit metastases, particularly dermal lesions, which are not amenable to complete surgical excision, intralesional local injections should be considered. Patients with least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions greater than 10 mm in diameter, may be appropriate candidates for intralesional injection with T-VEC. Intralesional injection with T-VEC is a recommended option patients with unresectable stage III in-transit disease based on improved durable and overall response rate compared to injection with GM-CSF alone. If T-VEC is not available, intralesional injection with IL-2 is another option, as are injection with BCG or IFN. All of these options are category 2B recommendations.

Based on noncomparative studies, laser ablation, topical imiquimod, or RT are category 2B options that may help for palliation or to establish regional control for selected patients with unresectable in-transit disease. Topical imiquimod can considered an option in very low volume cutaneous metastases.

For patients with multiple regional in-transit metastases confined to an extremity, regional chemotherapy by hyperthermic perfusion or infusion is an option. Although ILP and ILI can be technically challenging, they can result in high initial and durable regional response rates when administered properly.

With the advent of more effective systemic therapy, this approach is increasingly considered a first-line treatment option for regionally recurrent melanoma. See "Systemic Therapy for Advanced Melanoma," available in the complete version of these guidelines at NCCN.org, for treatment options. Given the number of options available, clinical judgement and multidisciplinary consultation is often helpful to determine the order of therapies.

Summary

The NCCN Guidelines for Melanoma represent an effort to distill and simplify an enormous body of knowledge and experience into fairly simple management algorithms. In general, treatment recommendations for primary tumors are based on better data than the recommendations for treating recurrent disease. These guidelines are intended as a point of departure, recognizing that all clinical decisions about individual patient management must be tempered by the clinician's judgment and other factors, such as local resources and expertise as well as the individual patient's needs, wishes, and expectations. Furthermore, the NCCN Guidelines for Melanoma undergo annual revision and are continually updated as new data become available.

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Individual Disclosures of the NCCN Melanoma Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Alain Algazi, MD	Acerta Pharma; Amgen Inc.; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Corvus Pharmaceuticals, Inc.; GlaxoSmithKline; MedImmune Inc.; Merck & Co., Inc.; and Novartis Pharmaceuticals Corporation	Taylor Blessey LLC	None	8/4/15
Robert Andtbacka, MD	Amgen Inc.	Amgen Inc.; and Merck & Co., Inc.	None	11/9/15
Christopher K. Bichakjian, MD	None	None	None	11/6/15
William E. Carson III, MD	National Cancer Institute	None	None	11/6/15
Daniel G. Coit, MD	None	None	None	3/24/16
Gregory A. Daniels, MD, PhD	Amgen Inc.; Bristol-Myers Squibb Company; Caladrius Biosciences, Inc.; Genentech, Inc.; and Prometheus Laboratories Inc.	None	None	11/8/15
Dominick DiMaio, MD	None	None	None	11/12/15
Marc A. Ernstoff, MD	Melanoma Research Alliance	None	None	6/5/15
Ryan C. Fields, MD	Washington University	None	None	11/6/15
Martin D. Fleming, MD	None	Amgen Inc.	None	11/6/15
Rene Gonzalez MD	Amgen Inc.; Bayer HealthCare; Bristol-Myers Squibb Company; Castle Biosciences, Inc.; Eisai Inc.; Genentech, Inc.; GlaxoSmithKline; Hana Biosciences, Inc.; Merck & Co., Inc.; Millennium Pharmaceuticals, Inc.; Morphotek Inc.; NeoStem, Inc.; Novartis Pharmaceuticals Corporation; Polynoma LLC; Prometheus Laboratories Inc.; Roche Laboratories, Inc.; and Takeda Pharmaceuticals North America, Inc.	Amgen Inc.; Bayer HealthCare; Castle Biosciences, Inc.; and Genentech, Inc.	None	6/4/15
Valerie Guild, MBA	None	None	None	11/6/15
Allan C. Halpern, MD	Janssen Research & Development, LLC; and Quintiles Inc.	Caliber Imaging & Diagnostics, Inc.; Canfield Scientific, Inc.; DermTech, Inc.; Emerald Medical Applications; Novartis Pharmaceuticals Corporation; and SciBase	None	6/5/15
F. Stephen Hodi Jr, MD[a]	Bristol-Myers Squibb; Genentech, Inc.; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	Amgen Inc.; Bristol-Myers Squibb Company; Merck & Co., Inc.; and Novartis Pharmaceuticals Corporation	Amgen Inc.; Bristol-Myers Squibb Company; Genentech, Inc.; GlaxoSmithKline; Merck & Co., Inc.; and Novartis Pharmaceuticals Corporation	6/5/15
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Julie R. Lange, MD, ScM	None	None	None	11/7/15
Mary C. Martini, MD	DermTech, Inc.	Dove - Unilever	None	11/3/15
Miguel A. Materin, MD	None	Back Bay Life Science Advisors; Trial case	None	11/22/15
Anthony J. Olszanski, MD	Amgen Inc.; Eli Lilly and Company; Merck & Co., Inc.; Pfizer Inc.; and Takeda Pharmaceuticals North America, Inc.	Merck & Co., Inc.	None	11/6/15
Merrick I. Ross, MD	None	Amgen Inc.; Genomic Health, Inc.; GlaxoSmithKline; Merck & Co., Inc.; and Provectus Biopharmaceuticals, Inc.	Amgen Inc.; GlaxoSmithKline; Merck & Co., Inc.; and Provectus Biopharmaceuticals, Inc.	11/6/15
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Jeff Sosman, MD	None	Amgen Inc.; and Genentech, Inc.	Amgen Inc.; and Genentech, Inc.	6/5/15
Susan M. Swetter, MD	None	None	None	3/11/16
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John A. Thompson, MD	Agensys, Inc.; Bristol-Myers Squibb Company; Genentech, Inc.; Merck & Co., Inc.; Pfizer Inc.; and Seattle Genetics	Celldex Therapeutics; Eisai Inc.; and Genentech, Inc.	None	11/11/15
Javier F. Torres-Roca, MD[a]	Cvergenx, Inc	None	None	11/10/15
Vijay Trisal, MD	None	None	None	11/7/15
Marshall M. Urist, MD	MSLT 2 Trial	Myriad Genetic Laboratories, Inc.	None	11/11/15

[a]The following individuals have disclosed that they have an Employment/ Governing Board, Patent, Equity, or Royalty conflict:
F. Stephen Hodi Jr, MD: Bristol-Myers Squibb Company
Kenneth Tanabe, MD: Helix12
Javier Torres-Roca, MD: Cvergenx, Inc.