National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Melanoma

Version 3.2016

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NCCN Guidelines Version 3.2016 Panel Members
Melanoma

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 3.2016 Updates
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Discussion

Updates in Version 3.2016 of the NCCN Guidelines for Melanoma from Version 2.2016 include:

Global Changes:

- **Workup language revised for various stages: "Imaging (CT scan PET/CT, MRI) to evaluate specific signs or symptoms" changed to "*Recommend* imaging ~~(CT scan PET/CT, MRI)~~ only to evaluate specific signs or symptoms."**
- **Footnote "i" was added to clarify recommended modalities wherever imaging is mentioned: "*Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.*"**

ME-5

- **After Primary Treatment, the recomendation "*Imaging to assess treatment response*" was added.**

ME-7 (Follow-up)

- **Stage IA-IIA-NED:**
  - **Third bullet revised, "Routine ~~radiologic~~ imaging to screen for asymptomatic..."**
  - **New bullet added: "*Recommend imaging as indicated to investigate specific signs or symptoms.*" This statement was previously part of footnote "dd" "Common Follow-up Recommendations for All Patients." Change was also made for Stage IIB-IV NED follow-up recommendadations on page ME-8.**

ME-8 (Follow-up)

- **Stage IIB-IV NED: Revised "Consider ~~chest x-ray, CT, brain MRI, and/or PET/CT scans~~ imaging every 3–12 mo (unless otherwise mandated by clinical trial participation) to screen for recurrent/metastatic disease (category 2B)". Footnote "i" also added.**
- **Footnote "gg" is new: "*Consider chest x-ray for surveillance of lung metastases*."**

ME-9

- **Local, satellite, and/or in-transit recurrence pathway**
  - **Workup recommendations revised:**
    - **"~~Recommend~~ *Consider* ~~baseline~~ imaging for *baseline* staging (category 2B)."**
    - **Recommend imaging to evaluate specific signs or symptoms ~~(category 2B)~~ ~~(CT scan, PET/CT, MRI)~~"**
  - **After "Treatment of recurrence," "*Imaging to assess treatment response*" was added.**

ME-10

- **Workup for nodal recurrence: Recommendation revised: "Recommend imaging for baseline staging and to evaluate specific signs or symptoms ~~(category 2B)~~ ~~(CT scan, PET/CT, MRI)~~."**

ME-11

- **Workup recommendation revised: "Recommend ~~CT chest/abdomen/pelvis ± MRI brain, and/or PET/CT~~ *imaging* for baseline staging and to evaluate specific signs and symptoms." Footnote "i" added.**
- **Limited (Resectable) pathway;**
  - **Treatment of Recurrence: Revised recommendation, "Resect or Observe or Systemic therapy~~; then repeat scans~~."**
  - **"*Imaging to assess response or progression*" was added after "Observe or Systemic therapy."**

MS-1

- **The Discussion text has been updated to reflect the changes in the algorithm.**

Continued

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Updates in Version 2.2016 of the NCCN Guidelines for Melanoma from Version 1.2016 include:

ME-4

- Adjuvant treatment: "*High-dose ipilimumab (category 2B)*" added as an option for Stage III (sentinel node positive) and Stage III (clinically positive node[s]).
- Footnote s is new: "*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.*"
- Footnote t is new: "*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.*"

ME-5

- Primary Treatment for Stage III in-transit: "*Intralesional injection with talimogene laherparepvec (T-VEC) (category 1)*" added as an option with corresponding footnote 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.*"

ME-8

- Treatment of Local, Satellite, and/or In-transit Recurrence: "*Intralesional injection with T-VEC (category 1)*" added as an option with corresponding footnote z.

ME-9

- Treatment of nodal recurrence with unresectable or systemic disease:
  - "Systemic therapy" is now listed as a "*preferred*" option.
  - Recommendation revised, "*Palliative* RT."
  - "*Intralesional injection with T-VEC*" added as an option with corresponding footnote z.
- Adjuvant Treatment for patients who have had a complete lymph node dissection and/or a complete resection of the nodal recurrence:
  - "*High-dose ipilimumab (category 2B)*" added as a treatment option with corresponding footnote s.
  - "Biochemotherapy" revised as follows "Biochemotherapy ~~for stages IIIB, IIIC~~."

ME-10

- Treatment for patients with disseminated (unresectable) distant metastatic disease:
  - "Systemic therapy" is now listed as a "preferred" option.
  - "*Intralesional injection with T-VEC*" added as an option for select patients with corresponding footnote ii "*T-VEC has shown a response rate (lasting ≥6 months) of 16% in highly selected patients with Stage IV-M1a disease (skin, subcutaneous, and/or remote nodes).*"

ME-E (1 of 6) Systemic Therapy for Metastatic or Unresectable Disease

- For both first-line and second-line or subsequent targeted therapy, the recommended combination regimens are listed as "preferred" over single-agent therapy options.
- First-line Therapy: "*Vemurafenib/cobimetinib (category 1)*" added as a preferred treatment option.
- Second-line or Subsequent Therapy: "*Vemurafenib/cobimetinib*" added as a treatment option
- Footnote 3 revised: "Nivolumab/ipilimumab combination therapy is associated with improved relapse-free survival compared with single-agent nivolumab or ipilimumab, at the expense of significantly increased toxicity. Compared to single-agent therapy, the impact of nivolumab/ipilimumab combination therapy on overall survival is not known. The phase III trial of nivolumab*/ipilimumab* ~~alone~~ versus *either nivolumab or* ~~nivolumab/~~ipilimumab *monotherapy* ~~versus ipilimumab alone~~ was conducted in previously untreated patients with unresectable stage III or IV melanoma."
- Footnote 4 is new: "*In previously untreated patients with unresectable Stage IIIC or Stage IV disease, the combination of vemurafenib/cobimetinib was associated with improved PFS and response rate when compared to vemurafenib alone. The impact on overall survival compared to single-agent vemurafenib is unknown.*"
- New references added for vemurafenib/cobimetinib combination therapy.

ME-F Management of Toxicities Associated with Immunotherapy and Targeted Therapy

Page 1 of 2

- Immunotherapy: Under "Ipilimumab" the first bullet was revised, "For more information *and specific wording of the black box warning,* see the full prescribiing information (www.fda.gov)."

Page 2 of 2

- Targeted Therapy: Last bullet revised, "For more information on toxicities associated with dabrafenib *with or without* trametinib, or vemurafenib *with or without cobimetinib,* and for the management of these toxicities, see the full prescribing information (www.fda.gov)."

Continued

Updates in Version 1.2016 of the NCCN Guidelines for Melanoma from Version 3.2015 include:

Global Changes

- **The footnote describing when and how to perform mutational analysis has been revised. (ME-6, ME-7, ME-8, ME-9)**

ME-1

- **Footnote c revised: "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). ~~Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but is not recommended or patients who are otherwise NED.~~"**
- **Footnote d is new: "*In the absence of metastatic disease, BRAF testing of the primary cutaneous melanoma is not recommended.*"**
- **Footnote f revised: "~~Given lower reported rates of SLN positivity in pure desmoplastic melanoma, it is important that an experienced dermatopathologist examine the entire lesion before making the decision to perform a SLNB.~~ *There is uncertainty regarding the diagnostic criteria for, the probability of a positive sentinel node in, and the prognostic significance of the sentinel node in pure desmoplastic melanoma. Multidisciplinary consultation including a dermatopathologist is recommended for determining staging and treatment options.* ~~(Busam KJ. Desmoplastic Melanoma. Clin Lab Med 2011;31:321-330.)~~"**

ME-2

- **"Clinical Stage" revised: "Stage IA, *IB* (≤0.75 mm thick, *any features)* ~~no ulceration, mitotic rate 0 per mm²); Stage IB (≤0.75 mm thick with ulceration, and/or mitotic rate ≥1 per mm²~~."**
- **Footnote j revised: "SLNB is an important staging tool, ~~but the impact of SLNB on overall survival is unclear~~ *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*."**

ME-3

- **"Clinical Stage" revised: "Stage IB (0.76–1.0 mm thick with ulceration or mitotic rate ≥1 per mm²) or Stage IB or *II* (>1 mm thick, any ~~characteristic~~ *feature*, N0)."**

ME-4

- **Stage III (sentinel node positive)**
  - **Primary Treatment: Recommendation revised, "*Discuss and offer* complete lymph node dissection."**
  - **Adjuvant Treatment: Interferon alfa changed from category 2B to category 2A.**
- **Stage III (clinically positive node[s])**
  - **Workup: Bullet revised, "FNA preferred, if feasible, or *core, incisional, or excisional biopsy* ~~lymph node biopsy~~."**
  - **Primary Treatment: Recommendation revised, "...complete *therapeutic* lymph node dissection."**
  - **Adjuvant Treatment:**
    - ◊ **Interferon alfa changed from category 2B to category 2A.**
    - ◊ **Biochemotherapy (category 2B) added as an option.**
    - ◊ **Recommendation revised, "...Consider RT to nodal basin in selected *high-risk* patients based on location..." (Also for ME-9)**

Continued

ME-4 (continued)

- **Footnote u is new: "*For a list of biochemotherapy regimens, See Other Systemic Therapies (ME-E 2 of 6).*"**
- **Footnote q revised: "~~The impact of complete lymph node dissection in patients with stage III (sentinel node positive) patients is unknown. This will be clarified when results of MSLT-II are published.~~ *CLND contributes to staging. Its impact on regional disease control and overall survival is the focus of ongoing clinical trials. Factors that 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)."**
- **Footnote r revised: "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)~~ *but there is no impact on overall survival*." (Also for ME-9)**
- **Footnote t revised: "Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has ~~no impact on~~ *shown no improvement* in relapse-free or overall survival.~~, and~~ Its benefits must be weighed against *potential toxicities* ~~the increased probability of long-term skin and regional toxicities and potential reduced quality of life~~."**

ME-5

- **Fourth column: After "Primary Treatment" the statement "If free of disease" was divided into two pathways "If free of disease *by surgery*" and "*If free of disease by other treatments.*" For the latter, "Clinical trial" or "Observation" are recommended as adjuvant treatment options.**

ME-6

- **Footnote y revised: "...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 ~~tissue~~ *mutation status* is relevant to eligibility for participation in a clinical trial."**

ME-7

- **Follow-up for Stage IIB-IV NED**
  - **Third bullet revised: "Consider chest x-ray, CT, *brain MRI,* and/or PET/CT scans..."**
  - **Recommendation removed: "Consider brain MRI annually (category 2B)"**
- **Footnote aa revised: "The frequency of follow-up and intensity of cross-sectional imaging should be based on the conditional probability of recurrence at any point in time after initial treatment. *Follow-up recommendations listed here are for surveillance for recurrence in patients with no evidence of disease.*"**

Continued

ME-8

- **Local, satellite, and/or in-transit recurrence**
  - **Workup: First bullet revised, "~~FNA or biopsy~~ *FNA preferred, if feasible, or core, incisional, or excisional biopsy.*"**
  - **Fourth column after "Treatment of Recurrence" the statement "If free of disease" was divided into two pathways: "If free of disease *by surgery*" and "*If free of disease by other treatments*". For the latter, "Clinical trial" or "Observation" were recommended as adjuvant treatment options.**

ME-9

- **Nodal recurrence:**
  - **Workup**
    - **First bullet revised: "~~FNA (preferred) or lymph node biopsy~~ *FNA preferred, if feasible, or core, incisional, or excisional biopsy.*" Corresponding new footnote dd added: "*Biopsy preferred if recurrence is unresectable.*"**
    - **Bullet removed: "Pelvic CT if inguinofemoral nodes clinically positive."**
  - **Adjuvant Treatment:**
    - **Interferon alfa changed from category 2B to category 2A.**
    - **Biochemotherapy for stages IIIB, IIIC (category 2B) added as an option.**

ME-10

- **Distant metastatic disease**
  - **Workup**
    - **First bullet revised: "~~FNA (preferred) or lymph node biopsy~~ *FNA preferred, if initial resection is planned. Biopsy (core, excisional, or incisional) preferred if initial therapy is to be systemic*."**
  - **For disseminated (unresectable) disease with brain metastases, recommendation revised: "Consider *palliative* resection and/or..."**

ME-A Principles of Biopsy and Principles of Pathology

- **Footnote 3 revised: "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). ~~Mutational analysis is recommended if patients are being considered for either routine treatment or clinical trials, but is not recommended or patients who are otherwise NED.~~"**
- **Footnote "4" is new: "*In the absence of metastatic disease, BRAF testing of the primary cutaneous melanoma is not recommended.*"**

ME-C Principles of Complete Lymph Node Dissection

- **Second bullet revised: "In the groin, consider elective iliac and obturator lymph node dissection if clinically positive ~~superficial~~ *inguinofemoral* nodes or ≥3 ~~superficial~~ *inguinofemoral* nodes are positive (category 2B)."**

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ME-D Principles of Radiation Therapy for Melanoma
Page 1 of 3

- **"Regional disease" recommendation revised: "Adjuvant treatment in selected patients following resection of clinically appreciable nodes (category 2B) if ~~LDH <1.5 x upper limit of normal AND~~..."**
- **Footnote 1 revised: "Interactions between radiation therapy and systemic therapies (eg, *BRAF* inhibitors, ~~and~~ interferon alfa-2b*, immunotherapies, and checkpoint inhibitors*) need to be very carefully considered as there is potential for increased toxicity."**
- **Footnote 3 revised: "Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has ~~no impact on~~ *shown no improvement* in relapse-free or overall survival. Its benefits must be weighed against potential *toxicities* ~~the increased probability of long-term skin and regional toxicities and potential reduced quality of life~~."**
- **Footnote 4 revised: "Adjuvant whole brain radiation following resected melanoma brain metastasis is controversial and should be considered on an individual patient basis. ~~An ongoing randomized clinical trial (ANZMTG 01-07, ACTRN12607000512426, NCT01503827) is currently investigating adjuvant whole brain radiation (Fogarty G, Morton RL, Vardy J, et al. Whole brain radiotherapy after local treatment of brain metastases in melanoma patients--a randomised phase III trial. BMC Cancer. 2011;11:142.)~~."**

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- **Primary Disease: New reference added "*Hedblad MA, Mallbris L. Grenz ray treatment of lentigo maligna and early lentigo maligna melanoma. J Am Acad Dermatol 2012;67:60-68.*"**

ME-E Systemic Therapy For Metastatic or Unresectable Disease
Page 1 of 6

- **This section was reorganized and extensively revised including:**
  - **The "Metastatic or unresectable disease" treatment pathways for "*BRAF* V600 wild type" and "*BRAF* V600 mutant" were combined into one algorithm.**
  - **Nivolumab/ipilimumab was added to the list of options for "First-line therapy" and "Second-line or subsequent therapy."**

ME-E Systemic Therapy For Metastatic or Unresectable Disease
Page 1 of 6 (continued)

- **Footnote 3 is new: "*Nivolumab/ipilimumab combination therapy is associated with improved relapse-free survival compared with single agent nivolumab or ipilimumab, at the expense of significantly increased toxicity. Compared to single agent therapy, the impact of nivolumab/ipilimumab combination therapy on overall survival is not known. The phase III trial of nivolumab alone versus nivolumab/ipilimumab versus ipilimumab alone was conducted in previously untreated patients with unresectable stage III or IV melanoma.*"**
- **Footnote 5 is new: "Consider second-line agents if not used first-line and not of the same class.**

Page 2 of 6

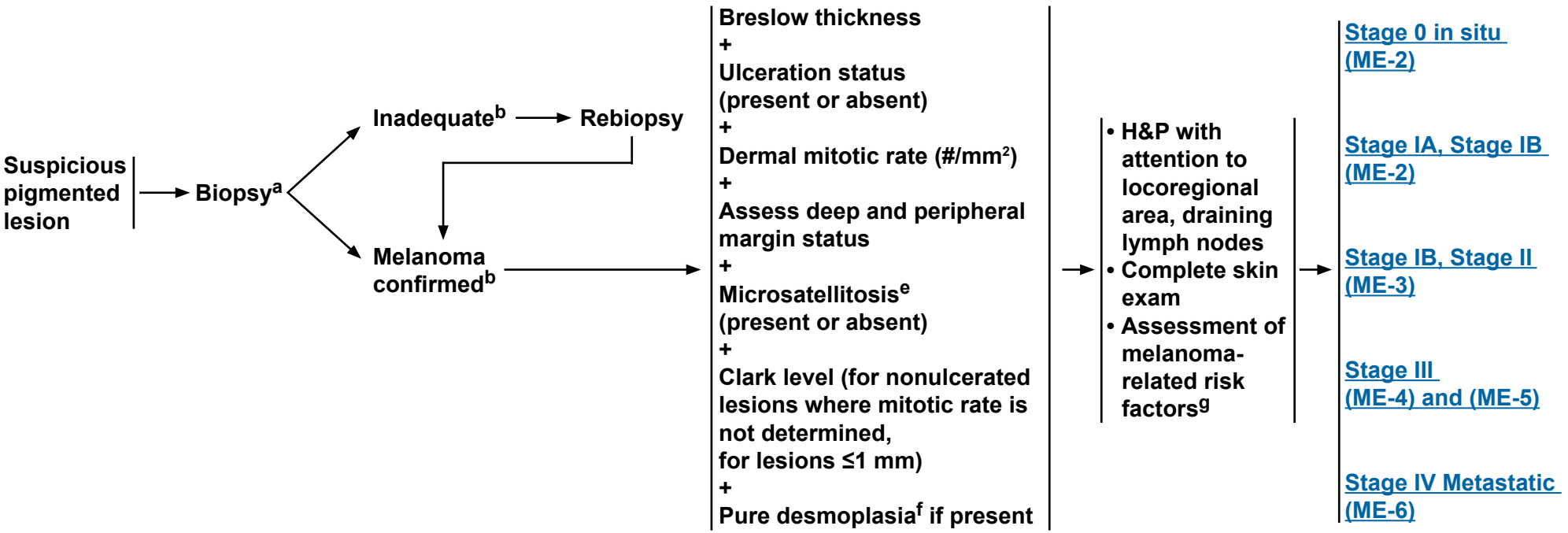
- **Page title changed from "Systemic Therapy for Metastatic or Unresectable Disease" to "*Other Systemic Therapies.*"**
- **Subheading title changed: "Cytotoxic Regimens *for Metastatic Disease.*"**
- **Subheading title changed: "Biochemotherapy *for Metastatic Disease.*"**
  - **This section was extensively revised.**
- **New section added: "*Biochemotherapy for Adjuvant Treatment of High-Risk Disease.*"**
  - **"*Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b (category 2B)*" added as the recommended regimen.**
- **Footnote 1 regarding cytotoxic regimens and biochemotherapy is new: "*In general, options for front-line therapy for metastatic melanoma include immunotherapy or targeted therapy.*"**

Page 3 of 6, Page 4 of 6, Page 5 of 6, and Page 6 of 6

The reference section was extensively revised to reflect the changes in the algorithm.

ME-F Management of Toxicities Associated with Immunotherapy and Targeted Therapy

- **This section was previously entitled "Principles of Immunotherapy and Targeted Therapy."**
- **This section was reorganized and extensively revised.**



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

[b] If diagnostic biopsy is inadequate for treatment decisions, rebiopsy may be appropriate.

[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).

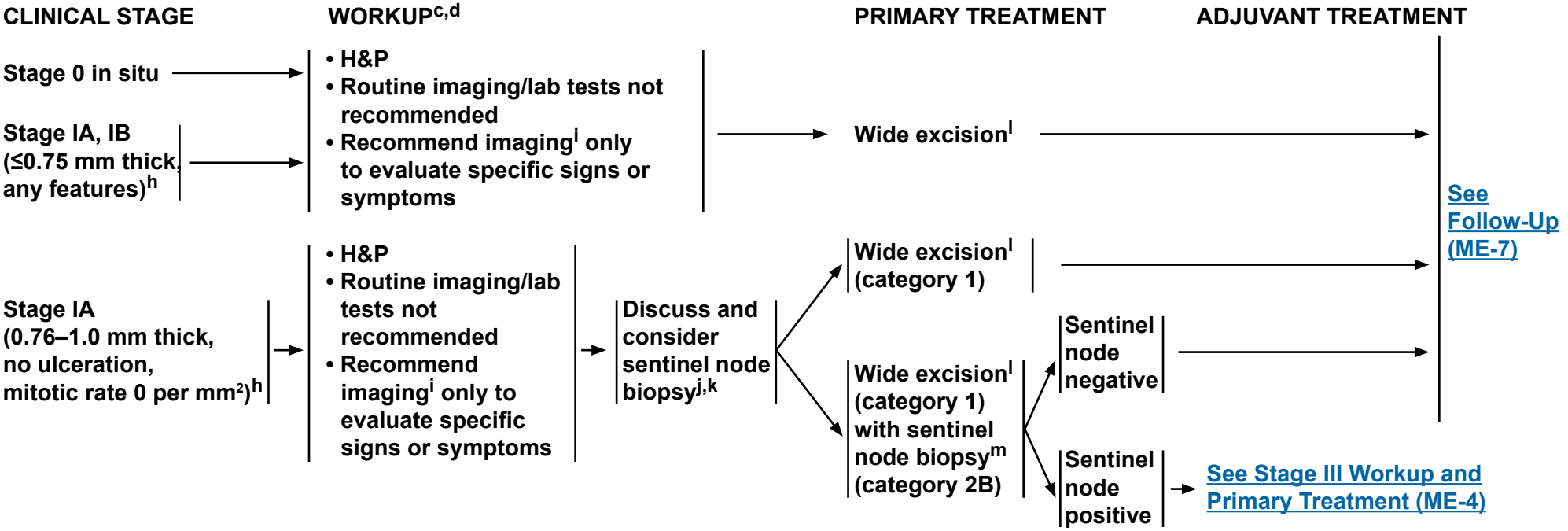
[d] In the absence of metastatic disease, *BRAF* testing of the primary cutaneous melanoma is not recommended.

[e] Microsatellitosis is defined in the CAP 2013 melanoma protocol (version 3.3.0.0) as “the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow measurement was taken" (Harrist TJ, Rigel DS, Day CL Jr, et al. “Microscopic satellites” are more highly associated with regional lymph node metastases than is primary melanoma thickness. Cancer 1984;53:2183-2187).

[f] There is uncertainty regarding the diagnostic criteria for, the probability of a positive sentinel node in, and the prognostic significance of the sentinel node in pure desmoplastic melanoma. Multidisciplinary consultation including a dermatopathologist is recommended for determining staging and treatment options.

[g] Risk factors for melanoma include family history of melanoma, prior primary melanoma, and other factors such as atypical moles/dysplastic nevi.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[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 lymphovascular invasion (LVI), are very uncommon in melanomas ≤0.75 mm thick. When present, SLNB may be considered on an individual basis.

[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 cutaneous melanoma is not recommended.

[i]Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

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

[k]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.

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

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

Note: All recommendations are category 2A unless otherwise indicated.
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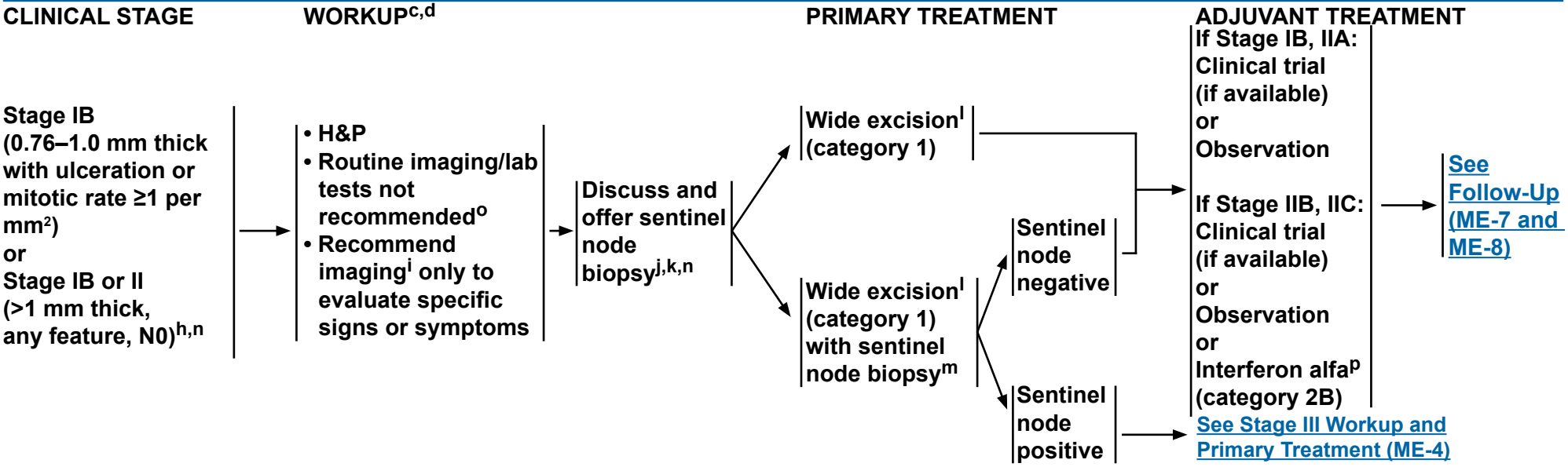


[h]In general, SLNB is not recommended for primary melanomas ≤0.75 mm thick, unless there is significant uncertainty about the adequacy of microstaging. For melanomas 0.76 to 1.0 mm thick, SLNB may be considered in the appropriate clinical context. In patients with thin melanomas (≤1.0 mm), apart from 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.

[n]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]Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

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

[k]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.

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

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

[o]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.

[p]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).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL/ PATHOLOGIC STAGE	WORKUP[q]	PRIMARY TREATMENT	ADJUVANT TREATMENT
Stage III (sentinel node positive)	• Consider imaging[i] for baseline staging (category 2B) • Recommend imaging[i] to evaluate specific signs or symptoms	Discuss and offer complete lymph node dissection[r]	Clinical trial or Observation or Interferon alfa[s] or High-dose ipilimumab[t,u] (category 2B)
Stage III (clinically positive node[s])	• FNA preferred, if feasible, or core, incisional, or excisional biopsy • Recommend imaging[i] for baseline staging and to evaluate specific signs or symptoms	Wide excision of primary tumor[l] (category 1) + complete therapeutic lymph node dissection	Clinical trial or Observation or Interferon alfa[s] or High-dose ipilimumab[t] (category 2B) or Biochemotherapy[v] (category 2B) and/or Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, and/or macroscopic extranodal extension[w,x] (category 2B)

(See Follow-up (ME-8))

[i] Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

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

[q] 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.

[r] CLND contributes to staging. Its impact on regional disease control and overall survival is the focus of ongoing clinical trials. Factors that 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).

[s] 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.

[t] 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.

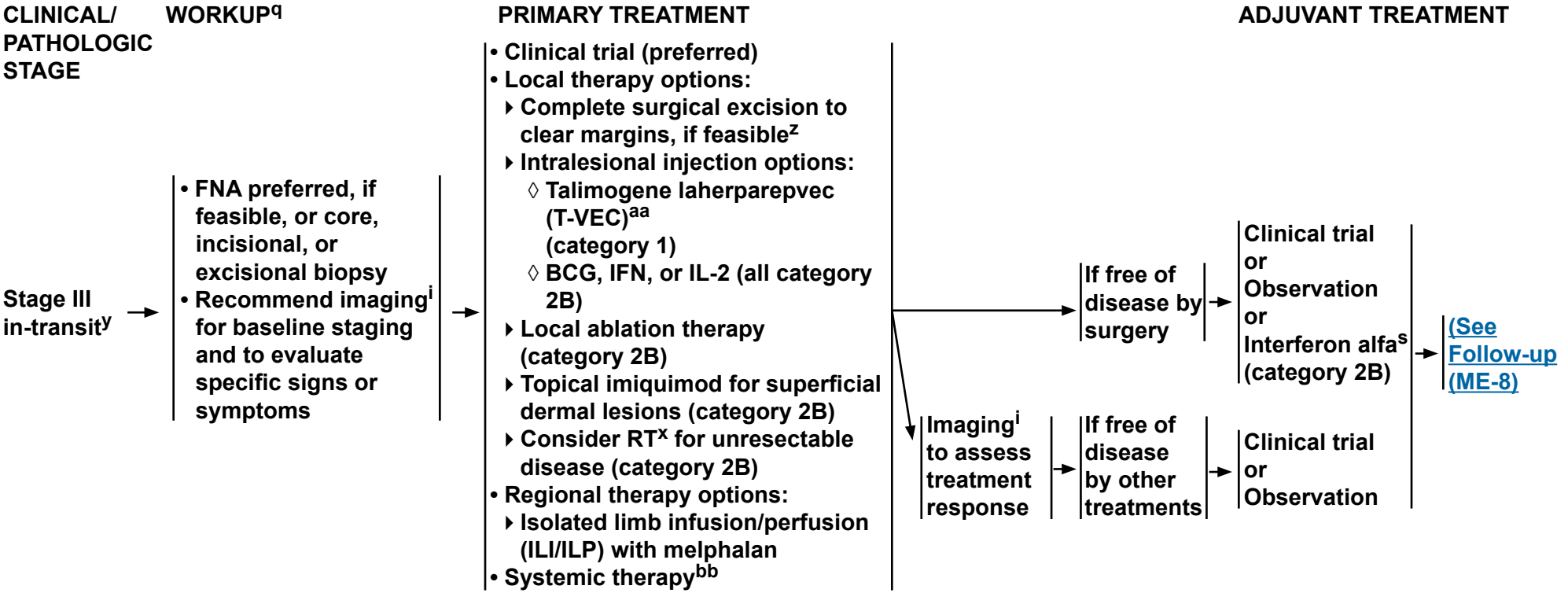
[u] The clinical trial excluded patients with sentinel lymph node metastases ≤1 mm in size and who did not undergo CLND. The decision to use ipilimumab should be based on risk of recurrence balanced against the risk of treatment-related toxicity. It is unclear whether the decision should be based on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

[v] For biochemotherapy, see Other Systemic Therapies (ME-E 2 of 6).

[w] 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.

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[i]Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

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

[s]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.

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

[y]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])

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

[aa]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.

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

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CLINICAL/ PATHOLOGIC STAGE

WORKUP

Stage IV Metastatic →

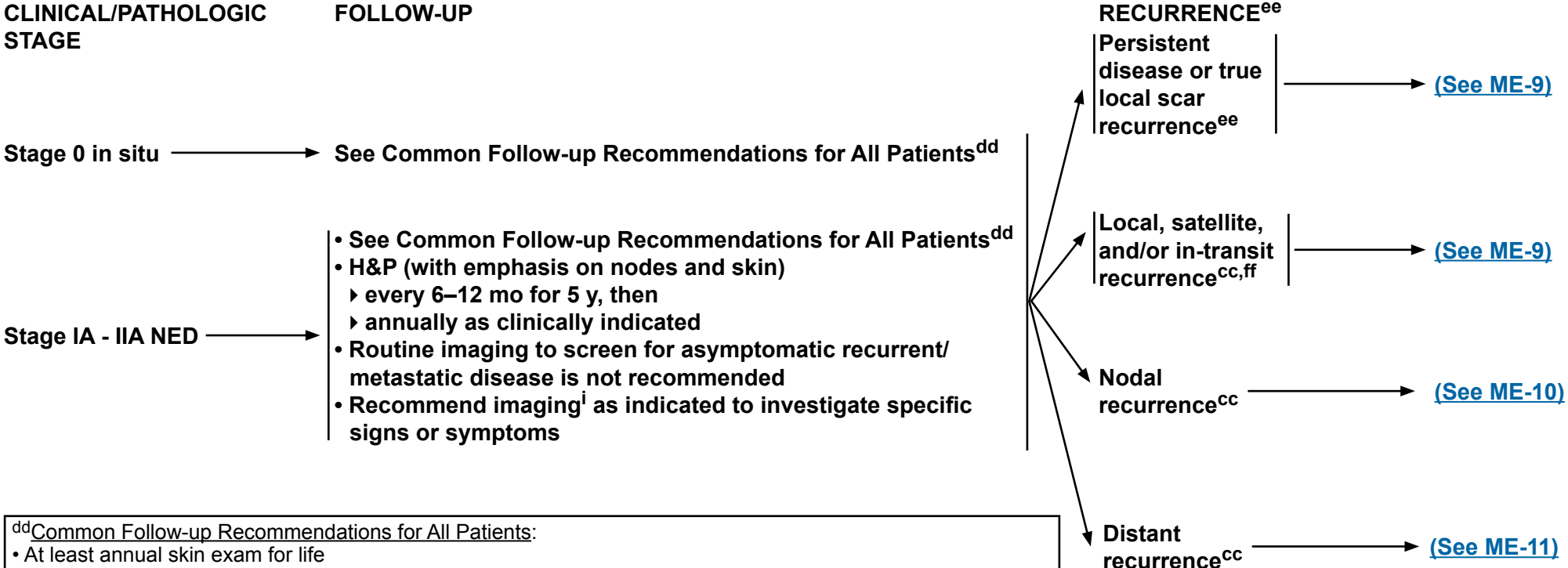
- **Biopsy preferred over FNA if archival tissue not available for genetic analysis[cc]**
- **LDH**
- **Recommend imaging[i] for baseline staging and to evaluate specific signs and symptoms**

→ **See Treatment for Limited (Resectable) or Disseminated (Unresectable) Disease (ME-11)**

[i]Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast (if clinically indicated). Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

[cc]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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[dd]Common Follow-up Recommendations for All Patients:
- At least annual skin exam for life
- Educate patient in regular self skin and lymph node exam
- Routine blood tests are not recommended
- Regional lymph node ultrasound may be considered in patients with an equivocal lymph node physical exam, patients who were offered but did not undergo SLNB, patients in whom SLNB was not possible (or not successful), or patients with a positive SLNB who did not undergo complete lymph node dissection (CLND). At this point, nodal basin ultrasound has not been shown to be a substitute for SLNB or CLND.
- Follow-up schedule is influenced by risk of recurrence, prior primary melanoma, and family history of melanoma, and includes other factors such as atypical moles/dysplastic nevi and patient/physician concern.

[i]Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

[cc]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.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL/PATHOLOGIC STAGE

FOLLOW-UP

Stage IIB - IV NED →

- **See Common Follow-up Recommendations for All Patients[dd]**
- **H&P (with emphasis on nodes and skin)**
  - **every 3–6 mo for 2 y, then**
  - **every 3–12 mo for 3 y, then**
  - **annually as clinically indicated**
- **Recommend imaging[i] as indicated to investigate specific signs or symptoms**
- **Consider imaging[i,gg] every 3–12 mo[hh] (unless otherwise mandated by clinical trial participation) to screen for recurrent/metastatic disease (category 2B)**
- **Routine imaging to screen for asymptomatic recurrent/metastatic disease is not recommended after 3–5 years**

RECURRENCE[ee]

- **Persistent disease or true local scar recurrence[ee]** → **(See ME-9)**
- **Local, satellite, and/or in-transit recurrence[cc,ff]** → **(See ME-9)**
- **Nodal recurrence[cc]** → **(See ME-10)**
- **Distant recurrence[cc]** → **(See ME-11)**

[dd]Common Follow-up Recommendations for All Patients:
- At least annual skin exam for life
- Educate patient in regular self skin and lymph node exam
- Routine blood tests are not recommended
- Regional lymph node ultrasound may be considered in patients with an equivocal lymph node physical exam, patients who were offered but did not undergo SLNB, patients in whom SLNB was not possible (or not successful), or patients with a positive SLNB who did not undergo complete lymph node dissection (CLND). At this point, nodal basin ultrasound has not been shown to be a substitute for SLNB or CLND.
- Follow-up schedule is influenced by risk of recurrence, prior primary melanoma, and family history of melanoma, and includes other factors such as atypical moles/dysplastic nevi and patient/physician concern.

[i]Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

[cc]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]Consider chest x-ray for surveillance of lung metastases.

[hh]The frequency of follow-up and intensity of cross-sectional imaging should be based on the conditional probability of recurrence at any point in time after initial treatment. Follow-up recommendations listed here are for surveillance for recurrence in patients with no evidence of disease.

[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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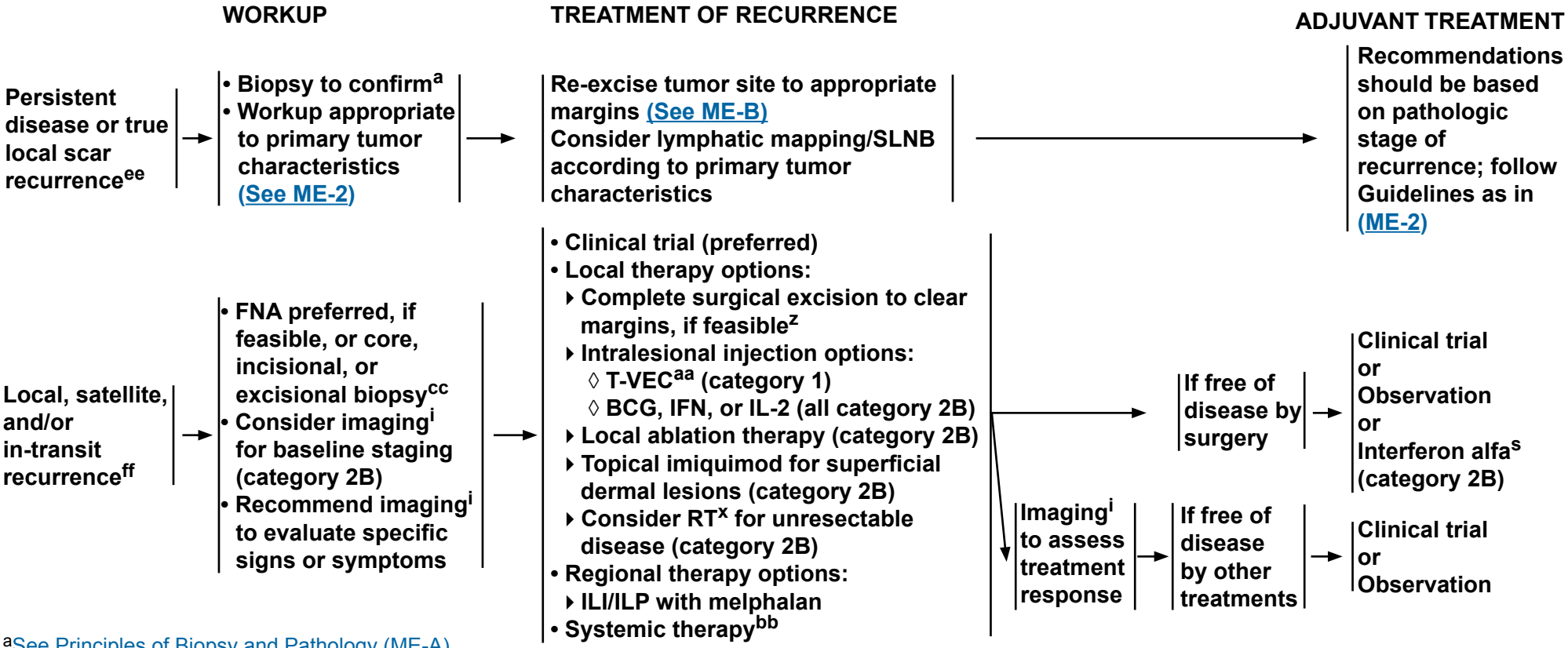

[a] See Principles of Biopsy and Pathology (ME-A).

[i] Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

[s] 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.

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

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

[aa] 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.

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

[cc] 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.

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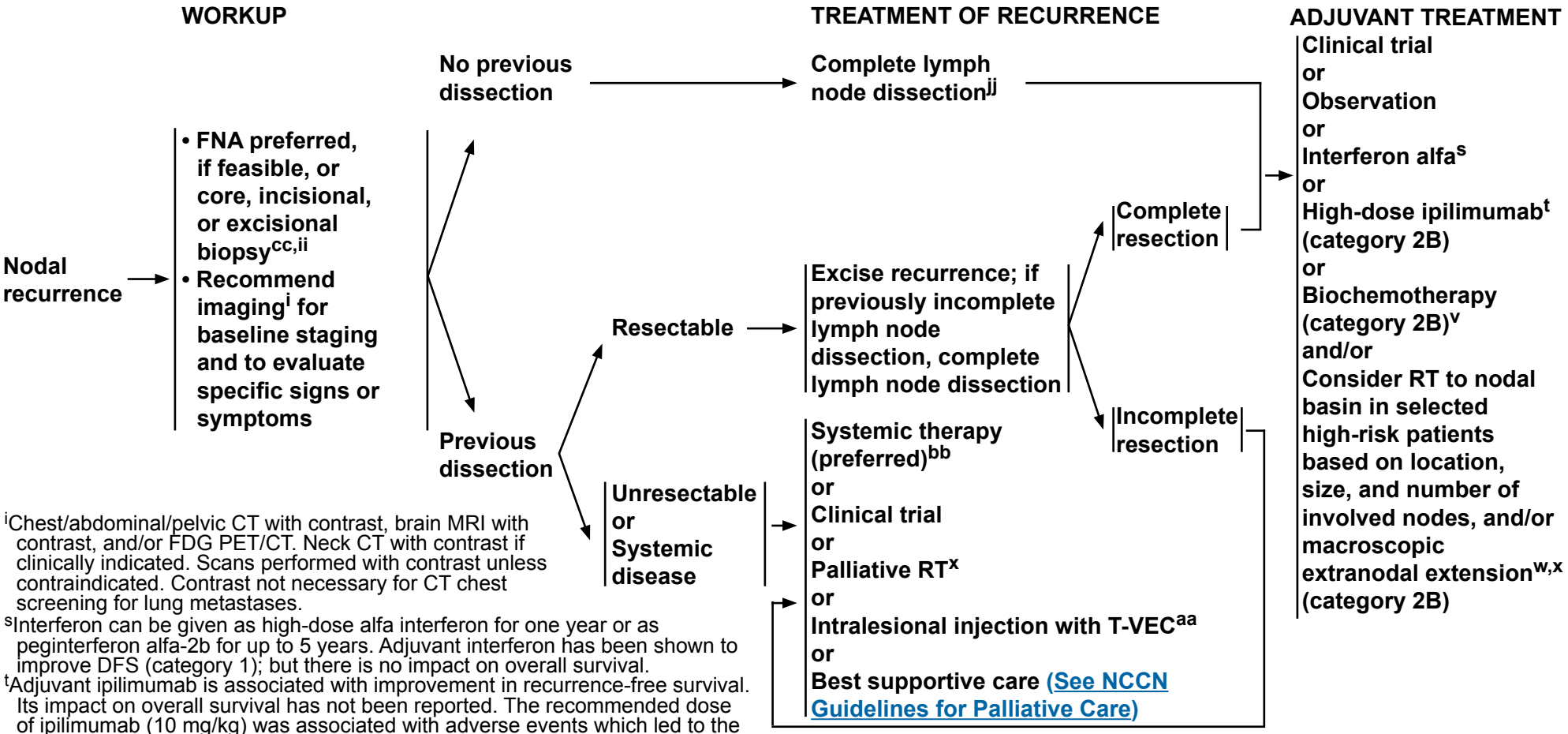

[i]Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

[s]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.

[t]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.

[v]For biochemotherapy, see Other Systemic Therapies (ME-E 2 of 6).

[w]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.

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

[aa]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.

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

[cc]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.

[ii]Biopsy preferred if recurrence is unresectable.

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

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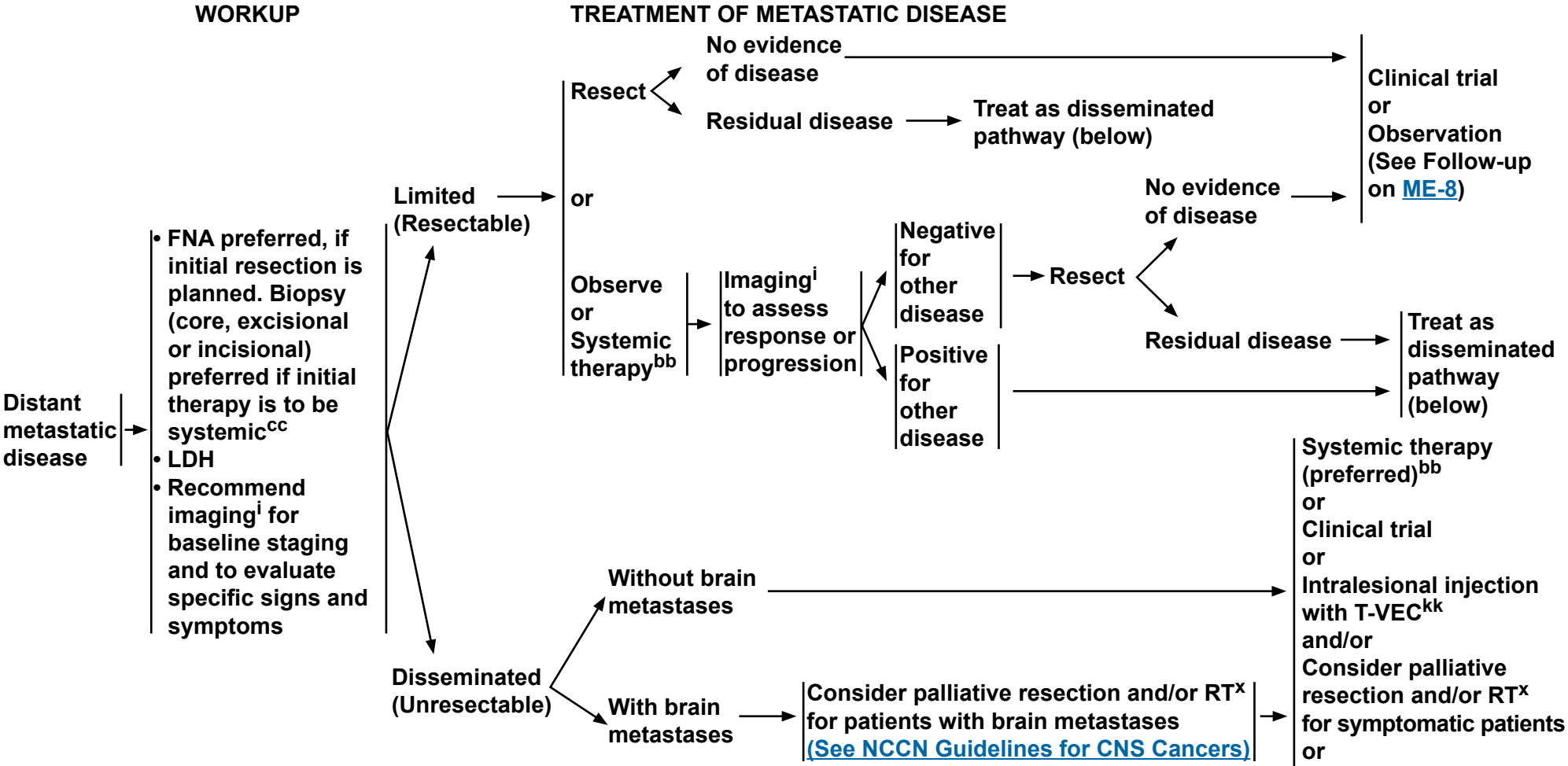

[i]Chest/abdominal/pelvic CT with contrast, brain MRI with contrast, and/or FDG PET/CT. Neck CT with contrast if clinically indicated. Scans performed with contrast unless contraindicated. Contrast not necessary for CT chest screening for lung metastases.

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

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

[cc]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.

[kk]T-VEC has shown a response rate (lasting ≥6 months) of 16% in highly selected patients with Stage IV-M1a disease (skin, subcutaneous, and/or remote nodes).

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PRINCIPLES OF BIOPSY

- **Excisional biopsy (elliptical, punch, or saucerization) with 1–3 mm margins preferred. Avoid wider margins to permit accurate subsequent lymphatic mapping.**
- **The orientation of the biopsy should be planned with definitive wide excision in mind (eg, parallel to lymphatics).**
- **Full-thickness incisional or punch biopsy[1] of clinically thickest portion of lesion acceptable, in certain anatomic areas (eg, palm/sole, digit, face, ear) or for very large lesions.**
- **Shave biopsy[1,2] may compromise pathologic diagnosis and complete assessment of Breslow thickness, but is acceptable when the index of suspicion is low.**

PRINCIPLES OF PATHOLOGY[3,4]

- **Biopsy to be read by a pathologist experienced in pigmented lesions.**
- **Minimal elements to be reported should include Breslow thickness (mm), histologic ulceration (present or absent), dermal mitotic rate per mm[2,5] Clark level (encouraged for lesions ≤1 mm, optional for lesions >1 mm), and peripheral and deep margin status of biopsy (positive or negative).**
- **Microsatellitosis (present or absent)[6]**
- **Encourage consistent reporting of these additional factors (compatible with American Academy of Dermatology recommendations[7]):**
  - **Location**
  - **Regression**
  - **Tumor-infiltrating lymphocytes (TILs)**
  - **Vertical growth phase (VGP)**
  - **Angiolymphatic invasion**
  - **Neurotropism**
  - **Histologic subtype**
  - **Pure desmoplasia, if present, or specify pure vs. mixed desmoplastic with spindle cell and/or epithelioid cells**
- **Consider use of comparative genomic hybridization (CGH) or fluorescence in situ hybridization (FISH) for histologically equivocal lesions.[8]**

[1]If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.

[2]For lentigo maligna melanoma in situ, a broad shave biopsy may help to optimize diagnostic sampling.

[3]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).

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

[5]Dermal mitotic rate should be determined using the "hot spot" technique and expressed as number of mitoses per square millimeter. (Piris A, Mihm Jr. MC, Duncan LM. AJCC melanoma staging update: impact on dermatopathology practice and patient management. J Cutan Pathol 2011;38:394-400).

[6]Microsatellitosis is defined in the CAP 2013 melanoma protocol (version 3.3.0.0) as "the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow measurement was taken" (Harrist TJ, Rigel DS, Day CL Jr, et al. "Microscopic satellites" are more highly associated with regional lymph node metastases than is primary melanoma thickness. Cancer 1984;53:2183-2187).

[7]Bichakjian C,Halpern AC, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol 2011;65:1032-1047.

[8]CGH may be more accurate than FISH in identifying relevant genetic mutations.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

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

- **Margins may be modified to accommodate individual anatomic or functional considerations.**

[1]For large melanoma in situ (MIS), lentigo maligna type, surgical margins >0.5 cm may be necessary to achieve histologically negative margins; techniques for more exhaustive histologic assessment of margins should be considered. For selected patients with positive margins after optimal surgery, consider topical imiquimod (for patients with MIS) or RT (category 2B).
[2]Excision recommendations are based on measured clinical margins taken at the time of surgery and not gross or histologic margins, as measured by the pathologist (category 1).

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PRINCIPLES OF COMPLETE LYMPH NODE DISSECTION

Adequacy of regional lymph node dissection:

- **An anatomically complete dissection[1] of involved nodal basin is required.**
- **In the groin, consider elective iliac and obturator lymph node dissection if clinically positive inguinofemoral nodes or ≥3 inguinofemoral nodes are positive (category 2B).**
- **Iliac and obturator lymph node dissection is indicated if pelvic CT is positive (category 2A) or if Cloquet's node is positive (category 2B).**
- **For primary melanomas of the head and neck with clinically or microscopically positive lymph nodes in the parotid gland, a superficial parotidectomy and appropriate neck dissection of the draining nodal basins is recommended.**

[1]Anatomic boundaries of lymph node dissection should be described in operative report.

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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 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)**
  - **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.

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Continue

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA
(References)

Primary Disease

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Regional Disease

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- Lee RJ, Gibbs JF, Proulx GM, Kollmorgen DR, et al. Nodal basin recurrence following lymph node dissection for melanoma: implications for adjuvant radiotherapy. Int J Radiat Oncol Biol Phys 2000;46:467-474.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continue

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA
(References)

Metastatic Disease

- Atkins MB, Sosman JA, Agarwala S, et al. Temozolomide, thalidomide, and whole brain radiation therapy for patients with brain metastasis from metastatic melanoma: a phase II Cytokine Working Group study. Cancer 2008;113: 2139-2145.
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- Sause WT, Cooper JS, Rush S, et al. Fraction size in external beam radiation therapy in the treatment of melanoma. Int J Radiat Oncol Biol Phys 1991;20:429-432.
- Anker CJ, Ribas A, Grossmann AH, et al. Severe liver and skin toxicity after radiation and vemurafenib in metastatic melanoma. J Clin Oncol 2013;31:e283-287.
- Peuvrel L, Ruellan AL, Thillays F, et al. Severe radiotherapy-induced extracutaneous toxicity under vemurafenib. Eur J Dermatol 2013;23:879.-881
- Fogarty G, Morton RL, Vardy J, et al. Whole brain radiotherapy after local treatment of brain metastases in melanoma patients--a randomised phase III trial. BMC Cancer 2011;11:142.

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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

Metastatic or unresectable disease →

FIRST-LINE THERAPY[1]

- Immunotherapy
  - Anti PD-1 monotherapy
    - ◊ Pembrolizumab[2]
    - ◊ Nivolumab (category 1)[2]
  - Nivolumab/ipilimumab[2,3]
- Targeted therapy if *BRAF* mutated; preferred if clinically needed for early response
  - Combination therapy (preferred)
    - ◊ Dabrafenib/trametinib[2] (category 1)
    - ◊ Vemurafenib/cobimetinib[2,4] (category 1)
  - Single-agent therapy
    - ◊ Vemurafenib (category 1)[2]
    - ◊ Dabrafenib (category 1)[2]
- Clinical trial

→ **Disease progression or Maximum clinical benefit from *BRAF* targeted therapy**

PERFORMANCE STATUS (PS)

PS 0–2 →

SECOND-LINE OR SUBSEQUENT THERAPY[5]

- Anti PD-1 monotherapy
  - Pembrolizumab[2]
  - Nivolumab[2]
- Nivolumab/ipilimumab[2,3]
- Ipilimumab (category 1)[2,6]
- Targeted therapy if *BRAF* mutated
  - Combination therapy (preferred)
    - ◊ Dabrafenib/trametinib[2]
    - ◊ Vemurafenib/cobimetinib[2,4]
  - Single-agent therapy
    - ◊ Vemurafenib[2]
    - ◊ Dabrafenib[2]
- High-dose IL-2[7]
- Biochemotherapy[8] (category 2B)
- Cytotoxic agents[8]
- Imatinib for tumors with activating mutations of *C-KIT*
- Clinical trial

PS 3–4 → **Consider best supportive care** (See NCCN Guidelines for Palliative Care)

[1]The choice of a treatment is based on evaluation of the individual patient.
[2]See Management of Toxicities of Immunotherapy and Targeted Therapy (ME-F)
[3]Nivolumab/ipilimumab combination therapy is associated with improved relapse-free survival compared with single-agent nivolumab or ipilimumab, at the expense of significantly increased toxicity. Compared to single-agent therapy, the impact of nivolumab/ipilimumab combination therapy on overall survival is not known. The phase III trial of nivolumab/ipilimumab versus either nivolumab or ipilimumab monotherapy was conducted in previously untreated patients with unresectable stage III or IV melanoma.
[4]In previously untreated patients with unresectable Stage IIIC or Stage IV disease, the combination of vemurafenib/cobimetinib was associated with improved PFS and response rate when compared to vemurafenib alone. The impact on overall survival compared to single-agent vemurafenib is unknown.
[5]Consider second-line agents if not used first line and not of the same class.
[6]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.
[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). Therapy should be restricted to an institution with medical staff experienced in the administration and management of these regimens.
[8]For a list of cytotoxic regimens and biochemotherapy regimens, see (ME-E 2 of 6).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

OTHER SYSTEMIC THERAPIES

Cytotoxic Regimens for Metastatic Disease[1]
- **Dacarbazine**
- **Temozolomide**
- **Paclitaxel**
- **Albumin-bound paclitaxel**
- **Carboplatin/paclitaxel**

Biochemotherapy for Metastatic Disease[1]
- **Dacarbazine or temozolomide, and cisplatin or carboplatin, with or without vinblastine or nitrosourea, and IL-2 and interferon alfa-2b (category 2B)**

Biochemotherapy for Adjuvant Treatment of High-Risk Disease
- **Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b (category 2B)**

[1]In general, options for front-line therapy for metastatic melanoma include immunotherapy or targeted therapy.

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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE (REFERENCES)

Immunotherapy

Pembrolizumab

- Ribas A, Puzanov I, Dummer R, et al. Pembrolizumab versus investigator-choice chemotherapy for ipilimumab-refractory melanoma (KEYNOTE-002): a randomised, controlled, phase 2 trial. Lancet Oncol 2015;16:908-918.
- Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med 2015;372:2521-2532.
- Robert C, Ribas A, Wolchok JD, et al. Anti-programmed-death-receptor-1 treatment with pembrolizumab in ipilimumab-refractory advanced melanoma: a randomised dose-comparison cohort of a phase 1 trial. Lancet 2014;384:1109-1117.
- Hamid O, Robert C, Daud A, et al. Safety and Tumor Responses with Lambrolizumab (Anti-PD-1) in Melanoma. N Eng J Med 2013;369:134-144.

Nivolumab

- Weber JS, D'Angelo SP, Minor D, et al. Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2015;16:375-384.
- Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med 2015;372:320-330.

Ipilimumab

- Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012;13:459-465.
- Weber JS, Kahler KC, Hauschild A. Management of Immune-Related Adverse Events and Kinetics of Response With Ipilimumab. J Clin Oncol 2012;30:2691-7.
- Hodi FS, O'Day SJ, McDermott DF, Weber RW, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Eng J Med 2010;363:711-723.
- Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517-2526.

Nivolumab/Ipilimumab

- Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med 2015;373:23-34.
- Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006-2017.

Note: All recommendations are category 2A unless otherwise indicated.
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Continue

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE (REFERENCES)

Targeted Therapy (Combination Therapy)

Dabrafenib/Trametinib

- Long GV, Stroyakovskiy D, Gogas H, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet 2015; 386:444-451.
- Robert C, Karaszewska B, Schachter J, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med 2015;372:30-39.
- Johnson DB, Flaherty KT, Weber JS, et al. Combined BRAF (Dabrafenib) and MEK inhibition (Trametinib) in patients with BRAFV600-mutant melanoma experiencing progression with single-agent BRAF inhibitor. J Clin Oncol 2014;32:3697-3704
- Sanlorenzo M, Choudhry A, Vujic I, et al. Comparative profile of cutaneous adverse events: BRAF/MEK inhibitor combination therapy versus BRAF monotherapy in melanoma. J Am Acad Dermatol 2014;71:1102-1109 e1101.

Vemurafenib/Cobimetinib

- Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371:1867-1876.
- Ribas A, Gonzalez R, Pavlick A, et al. Combination of vemurafenib and cobimetinib in patients with advanced BRAF(V600)-mutated melanoma: a phase 1b study. Lancet Oncol 2014;15:954-965.
- Pavlick AC, Ribas A, Gonzalez R, et al. Extended follow-up results of phase Ib study (BRIM7) of vemurafenib (VEM) with cobimetinib (COBI) in BRAF-mutant melanoma. ASCO Meeting Abstracts 2015;33:9020.

Targeted Therapy (Single-agent Therapy)

Vemurafenib

- Sosman JA, Kim KB, Schuchter L, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. N Engl J Med 2012;366:707-714.
- Chapman reference under Vemurafenib with: McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. Lancet Oncol 2014;15:323-332.

Dabrafenib

- Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13:1087-1095.
- Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet 2012;380:358-365.

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Continue

SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE (REFERENCES)

Targeted Therapy (Single-agent Therapy)

Imatinib for tumors with activating mutations of *C-KIT*

- Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol 2013;31:3182-3190.
- Carvajal RD, Antonescu CR, Wolchok, JD, et al. KIT as a therapeutic target in metastatic melanoma. JAMA 2011;395:2327-2334.

High-dose IL-2

- Rosenberg SA, Yang JC, Topalian SL, et al. Treatment of 283 consecutive patients with metastatic melanoma or renal cell cancer using high-dose bolus interleukin 2. JAMA 1994;271:907-913.
- Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999;17:2105-2116.
- Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. Cancer J Sci Am 2000;6 Suppl 1:S11-14.
- Smith FO, Downey SG, Klapper JA, et al. Treatment of metastatic melanoma using interleukin-2 alone or in conjunction with vaccines. Clin Cancer Res 2008;14:5610-5618.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continue

OTHER SYSTEMIC THERAPIES (REFERENCES)

Cytotoxic Regimens for Metastatic Disease

Dacarbazine

- Serrone L, Zeuli M, Sega FM, et al. Dacarbazine-based chemotherapy for metastatic melanoma: thirty-year experience overview. J Exp Clin Cancer Res 2000;19:21-34.

Temozolomide

- Middleton MR, Grob JJ, Aaronson N, et al. Randomized phase III study of temozolomide versus dacarbazine in the treatment of patients with advanced metastatic malignant melanoma. J Clin Oncol 2000;18:158-166.

Paclitaxel

- Wiernik PH and Einzig AI. Taxol in malignant melanoma. J Natl Cancer Inst Monogr 1993;15:185-187.

Albumin-bound paclitaxel

- Hersh EM, O'Day SJ, Ribas A, et al. A phase 2 Clinical trial of nab-Paclitaxel in previously treated and chemotherapy-naïve patients with metastatic melanoma. Cancer 2010;116:155-163.
- Kottschade LA, Suman VJ, Amatruda T, et al. A phase II trial of nab-paclitaxel (ABI-007) and carboplatin in patients with unresectable stage iv melanoma: a north central cancer treatment group study, N057E(1). Cancer 2011;117:1704-1710.

Paclitaxel/carboplatin

- Rao RD, Holtan SG, Ingle JN, et al. Combination of paclitaxel and carboplatin as second-line therapy for patients with metastatic melanoma. Cancer 2006;106:375-382.
- Agarwala SS, Keilholz U, Hogg D, et al. Randomized phase III study of paclitaxel plus carboplatin with or without sorafenib as second-line treatment in patients with advanced melanoma. J Clin Oncol (Meeting Abstracts). 2007;25(18_suppl):8510.
- Hauschild A, Agarwala SS, Trefzer U, et al. Results of a phase III, randomized, placebo-controlled study of sorafenib in combination with carboplatin and paclitaxel as second-line treatment in patients with unresectable stage III or stage IV melanoma. J Clin Oncol 2009;27:2823-2830.
- Flaherty KT, Lee SJ, Schuchter LM, et al. Final results of E2603: A double-blind, randomized phase III trial comparing carboplatin (C)/paclitaxel (P) with or without sorafenib (S) in metastatic melanoma. J Clin Oncol (ASCO Meeting Abstracts) 2010. 28:(suppl; abstr):8511.

Biochemotherapy for Metastatic Disease

Dacarbazine or temozolomide, and cisplatin or carboplatin, with or without vinblastine or nitrosourea, and IL-2 and interferon alfa-2b

- Legha SS, Ring S, Eton O, et al. Development of a biochemotherapy regimen with concurrent administration of cisplatin, vinblastine, dacarbazine, interferon alfa, and interleukin-2 for patients with metastatic melanoma. J Clin Oncol 1998;16:1752-1759.
- Eton O, Legha SS, Bedikian AY, et al. Sequential biochemotherapy versus chemotherapy for metastatic melanoma: results from a phase III randomized trial. J Clin Oncol 2002;20:2045-2052.
- O'Day SJ, Boasberg PD, Piro L, et al. Maintenance biotherapy for metastatic melanoma with interleukin-2 and granulocyte macrophage-colony stimulating factor improves survival for patients responding to induction concurrent biochemotherapy. Clin Cancer Res 2002;8:2775-2781.
- Ives NJ, Stowe RL, Lorigan P, Wheatley K. Chemotherapy compared with biochemotherapy for the treatment of metastatic melanoma: a meta-analysis of 18 trials involving 2,621 patients. J Clin Oncol 2007;25:5426-5434.
- Atkins MB, Hsu J, Lee S, et al. Phase III trial comparing concurrent biochemotherapy with cisplatin, vinblastine, dacarbazine, interleukin-2, and interferon alfa-2b with cisplatin, vinblastine, and dacarbazine alone in patients with metastatic malignant melanoma (E3695): a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2008;26:5748-5754.

Biochemotherapy for Adjuvant Treatment of High Risk Disease

Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b

- Flaherty LE, Othus M, Atkins MB, et al. Southwest Oncology Group S0008: a phase III trial of high-dose interferon Alfa-2b versus cisplatin, vinblastine, and dacarbazine, plus interleukin-2 and interferon in patients with high-risk melanoma--an intergroup study of cancer and leukemia Group B, Children's Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. J Clin Oncol 2014;32:3771-3778.

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MANAGEMENT OF TOXICITIES ASSOCIATED WITH IMMUNOTHERAPY AND TARGETED THERAPY

Immunotherapy

- **Anti-PD1 Agents (pembrolizumab or nivolumab)**
  - **Pembrolizumab and nivolumab may cause immune-mediated adverse reactions. Grade 3–4 toxicities are less common than with ipilimumab, but require similar expertise in management. The most common adverse events (>20% of patients) include fatigue, rash, pruritus, cough, diarrhea, decreased appetite, constipation, and arthralgia. Depending on the severity of the reaction, pembrolizumab and nivolumab should be discontinued.**
  - **For moderate to severe immune-mediated pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hyperthyroidism, anti-PD1 therapy should be discontinued and systemic steroids should be administered.**
  - **Immune-mediated dermatitis sometimes responds to topical corticosteroids. For patients who do not respond, consider referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of immunotherapy.**
  - **Infliximab 5 mg/kg is preferred for treatment of severe immune-related colitis that does not respond promptly (within 1 week) to therapy with high-dose steroids. A single dose of infliximab is sufficient to resolve immune-related colitis in most patients.**
  - **For patients with preexistent hypophysitis due to ipilimumab, pembrolizumab may be administered if patients are on appropriate physiologic replacement endocrine therapy.**
  - **For more information on toxicities associated with pembrolizumab and nivolumab and the management of these toxicities, see the full prescribing information (www.fda.gov).**
- **Ipilimumab**
  - **Ipilimumab has the potential for significant immune-mediated complications. Although no longer required by the FDA, the Risk Evaluation and Mitigation Strategy program and/or experience in use of the drug as well as resources to follow the patient closely are essential for safe use of ipilimumab. Patient management information may be viewed at (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM249435.pdf). For more information and specific wording of the black box warning, see the full prescribing information (www.fda.gov)**
  - **For moderate to severe immune-mediated toxicity, ipilimumab should be discontinued and systemic steroids should be administered. See the prescribing information (www.fda.gov)**
  - **Immune-mediated dermatitis sometimes responds to topical corticosteroids. For patients who do not respond, consider referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of immunotherapy.**
  - **Infliximab 5 mg/kg is preferred for treatment of severe immune-related colitis that does not respond promptly (within 1 week) to therapy with high-dose steroids. A single dose of infliximab is sufficient to resolve immune-related colitis in most patients.**
  - **For severe hepatotoxicity refractory to high-dose steroids, mycophenolate is preferred over infliximab as second-line therapy.**
  - **Ipilimumab should be used with extreme caution, if at all, in patients with serious underlying autoimmune disorders.**
- **Combination Therapy**
  - **Clinically significant (grade 3 and 4) immune-related adverse events are seen more commonly with nivolumab/ipilimumab combination therapy compared to ipilimumab or nivolumab monotherapy. This emphasizes the need for careful patient education, selection, and monitoring.**

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Continue

MANAGEMENT OF TOXICITIES ASSOCIATED WITH IMMUNOTHERAPY AND TARGETED THERAPY

Targeted Therapy (BRAF *or* combined BRAF/MEK inhibitors)

- **Dermatologic: Regular dermatologic evaluation and referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of targeted therapy is recommended. BRAF inhibitors are associated with cutaneous squamous cell carcinoma, extreme photosensitivity, and other dermatologic toxicities, which occur much less often with concurrent MEK inhibitors.**
- **Pyrexia: Pyrexia (defined as a temperature of 38.5 °C or greater) is a common (~55%) side effect of combining BRAF and MEK inhibitors and occurs less frequently with BRAF monotherapy (~20%). The pyrexia is episodic, and onset is often 2 to 4 weeks following the start of therapy with a median duration of 9 days. Pyrexia may be associated with chills, night sweats, rash, dehydration, electrolyte abnormalities, and hypotension. Stopping or holding dabrafenib and trametinib at the onset of pyrexia will often interrupt the episode, and treatment can be resumed with full-dose dabrafenib and trametinib upon cessation of pyrexia and pyrexia-related symptoms. Upon re-exposure to dabrafenib and trametinib, repeat pyrexia events can occur, but grade >3 events are uncommon (21%). In occasional instances of prolonged or severe pyrexia not responsive to discontinuation of dabrafenib and trametinib, low-dose steroids (prednisone 10 mg/day) can be used. Patients with pyrexia should be advised to use antipyretics as needed and increase fluid intake.**
- **For more information on toxicities associated with dabrafenib with or without trametinib, or vemurafenib with or without cobimetinib, and for the management of these toxicities, see the full prescribing information (www.fda.gov).**

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

Table 1

American Joint Committee on Cancer (AJCC)
TNM Staging System for Melanoma (7th ed., 2010)

Primary Tumor (T)

TX Primary tumor cannot be assessed (eg, curettaged or severely regressed melanoma)

T0 No evidence of primary tumor

Tis Melanoma *in situ*

T1 Melanomas 1.0 mm or less in thickness

T2 Melanomas 1.01–2.0 mm

T3 Melanomas 2.01–4.0 mm

T4 Melanomas more than 4.0 mm

Note: a and b sub categories of T are assigned based on ulceration and number of mitoses per mm^2 as shown below:

T classification	*Thickness (mm)*	*Ulceration Status/Mitoses*
T1	≤1.0	a: w/o ulceration and mitosis $<1/mm^2$ b: with ulceration or mitoses $\geq 1/mm^2$
T2	1.01–2.0	a: w/o ulceration b: with ulceration
T3	2.01–4.0	a: w/o ulceration b: with ulceration
T4	>4.0	a: w/o ulceration b: with ulceration

Regional Lymph Nodes (N)

NX Patients in whom the regional lymph nodes cannot be assessed (eg, previously removed for another reason)

N0 No regional metastases detected

N1-3 Regional metastases based upon the number of metastatic nodes and presence or absence of intralymphatic metastases (in transit or satellite metastases)

Note: N1-3 and a-c sub categories are assigned as shown below:

N Classification	*No. of Metastatic Nodes*	*Nodal Metastatic Mass*
N1	1 node	a: micrometastasis* b: macrometastasis**
N2	2–3 nodes	a: micrometastasis* b: macrometastasis** c: in transit met(s)/satellite(s) *without* metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) *with* metastatic node(s)	

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

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

Continue

Distant Metastasis (M)

M0	No detectable evidence of distant metastases
M1a	Metastases to skin, subcutaneous, or distant lymph nodes
M1b	Metastases to lung
M1c	Metastases to all other visceral sites or distant metastases to any site combined with an elevated serum LDH

Note: Serum LDH is incorporated into the M category as shown below:

M Classification	*Site*	*Serum LDH*
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Anatomic Stage/Prognostic Groups

Clinical Staging*

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	AnyT	≥N1	M0
Stage IV	Any T	Any N	M1

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

Pathologic Staging**

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T3a	N0	M0
Stage IIB	T3b	N0	M0
	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage IIIA	T(1–4)a	N1a	M0
	T(1–4)a	N2a	M0
Stage IIIB	T(1–4)b	N1a	M0
	T(1–4)b	N2a	M0
	T(1–4)a	N1b	M0
	T(1–4)a	N2b	M0
	T(1–4)a	N2c	M0
Stage IIIC	T(1–4)b	N1b	M0
	T(1–4)b	N2b	M0
	T(1–4)b	N2c	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

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

Discussion

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.

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Overview

In 2016, an estimated 76,380 patients will be diagnosed with and about 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 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.[1] 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 to 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 with or without 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 who 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] In the United States, it is estimated that 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] The likelihood of regional nodal involvement increases with increasing tumor thickness, as well as 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 quite distinct from 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, has made long-term remission possible for a larger proportion of patients.

There is increasing appreciation of the variations in specific genetic alterations among distinct clinical subtypes of melanoma. The currently described clinical subtypes of cutaneous melanoma are: non-chronic sun damage (non-CSD): melanomas on skin without chronic sun-induced damage; CSD: melanomas on skin with chronic sun-induced damage signified by the presence of marked solar elastosis; and acral: melanomas on the soles, palms, or sub-ungual sites. Melanocytes exist outside of the skin as well, and can give rise to non-cutaneous melanomas on mucosal membranes, the uveal tract of the eye, or leptomeninges.[20] Mucosal melanomas most often occur in the head and

neck sinuses and oral cavity, anorectum, vulva, and vagina, but can arise in any of the mucosal membranes lining the gastrointestinal and urogenital tracts.[21]

Different subtypes of melanoma have been found to have very different genetic profiles, some of which have different therapeutic implications. In an analysis of 102 primary melanomas, the non-CSD subtype was found to have the highest proportion of *BRAF* mutations (56%) compared to CSD, acral, and mucosal subtypes (6%, 21%, and 3%, respectively).[22] On the other hand, 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 National Comprehensive Cancer Network (NCCN) practice guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments. Exceptions to the rule were discussed among the panel members while developing these guidelines. A 5% rule (omitting specific recommendations for clinical scenarios that comprise less than 5% of all cases) was used to eliminate uncommon clinical occurrences or conditions from these guidelines. The NCCN Melanoma Panel strongly supports early diagnosis and appropriate treatment of melanoma, including participation in clinical trials where available.

Mucosal and uveal melanomas differ significantly from cutaneous melanoma in presentation, genetic profile, staging, response to treatment, and patterns of progression.[23-25] 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. 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.

Delivery of High-Quality Cancer Care

A key component to delivery of high-quality cancer care is discussing with patients their options for diagnostic workup, treatment, and follow-up.[26] The goal of these conversations should be two-fold: 1) capturing all the case-specific information that should be considered when evaluating options, and 2) ensuring that the patient understands all the potential benefits and risks associated with different clinical approaches so they can make informed decisions. Adherence to the guidelines does not mean limiting decisions about patient care exclusively to NCCN-recommended guidelines, but that all the recommended options are *discussed* with the patients. The clinical team should document the rationale for the clinical approach selected. An essential feature of high-quality care is that clinical decisions are informed by a variety of case-specific factors (eg, patient characteristics and preferences, disease characteristics, medical history), such that for some patients the best clinical approach may not be an option listed in the guidelines. The guidelines include language such as “discuss and consider” and “consider and offer” to indicate situations in which conversations with the patient are especially important because the optimal option is not clear (eg, insufficient clinical data) and/or strongly depends on case-specific factors (eg, data show that the approach is beneficial only to a

subset of patients with specific features). Whereas “discuss and consider” indicates that the recommended option may be beneficial for some patients, “consider and offer” indicates that the recommended approach is likely beneficial for most patients.

Clinical Presentation and Preliminary Workup

Biopsy: NCCN Recommendations

Patients presenting with a suspicious pigmented lesion optimally should undergo an excisional biopsy (elliptical, punch or saucerization), preferably with 1- to 3-mm negative margins. The orientation of the excisional biopsy should always be planned with definitive treatment in mind (eg, a longitudinal orientation in the extremities, parallel to lymphatics). With the increasing use of lymphatic mapping and sentinel node biopsy, biopsies should also be planned so as not to interfere with this procedure. In this regard, wider margins for the initial diagnostic procedure should be avoided.

Excisional biopsy may be inappropriate for certain sites (including the face, palmar surface of the hand, sole of the foot, ear, distal digit, or subungual lesions) or for very large lesions. In these instances, a full-thickness incisional or punch biopsy of the clinically thickest portion of the lesion is an acceptable option. These procedures should provide accurate primary tumor microstaging, without interfering with definitive local therapy. If the initial biopsy is inadequate to make a diagnosis or to accurately microstage the tumor (based on evaluation by a dermatopathologist) for treatment planning, re-biopsy with narrow margin excision should be considered. Shave biopsy may compromise pathologic diagnosis and complete assessment of Breslow thickness. However, it is acceptable in a low suspicion setting. For example, a broad shave biopsy may help to optimize accurate diagnosis of lentigo maligna. Panelists recognized that melanomas are commonly diagnosed by shave biopsy during screening in a dermatologist office, and that any diagnosis is better than none even if microstaging may not be complete.

Diagnosis, Prognostic Factors, and Clinical Staging

In general, cutaneous melanomas are categorized as follows: localized disease with no evidence of metastases (stage I–II), regional disease (stage III), and distant metastatic disease (stage IV). The AJCC analyzed 38,918 patients to determine factors significantly predictive of survival for patients with cutaneous melanomas.[14,27-29] This and other studies have shown that in addition to patient-specific factors of age and gender, tumor-specific factors of Breslow tumor thickness, ulceration, and mitotic rate were found to be the three most important characteristics independently predictive of outcome by multivariate analysis.[14,28-34]

Mitotic rate is an indicator of tumor proliferation and is measured as the number of mitoses per mm^2. The latest AJCC Staging Manual recommended the “hot spot” technique for calculating the mitotic rate.[27,35] Several other studies have also confirmed the prognostic importance of mitotic rate in patients with primary cutaneous melanoma.[28-33,36-40] In the evidence-based derivation of the 2010 AJCC staging system, mitotic rate greater than or equal to 1 per mm^2 was independently associated with worse disease-specific survival (DSS), especially in patients with melanoma less than or equal to 1.0 mm thick.[14] As such, mitotic rate has replaced Clark level as a criterion for upstaging patients with melanomas less than or equal to 1.0 mm in thickness from IA to IB.

Reporting detection of microscopic satellites in the initial biopsy or wide excision specimen is also important for AJCC staging, as this defines at least N2c, stage IIIB disease. The 2013 College of American

Pathologists have defined a microsatellite as the presence of tumor nests greater than 0.05 mm in diameter, in the reticular dermis, panniculus, or vessels beneath the principal invasive tumor but separated from it by at least 0.3 mm of normal tissue on the section in which the Breslow measurement was taken.[41,42] It is usually not possible to detect microscopic satellites with less than a complete excisional biopsy.

The American Academy of Dermatology (AAD) Task Force recommends the inclusion of additional factors such as vertical growth phase (VGP), tumor-infiltrating lymphocytes (TIL), and regression in the report.[43,44] These factors are less consistently independently predictive of outcome.[31,32,45,46]

The AAD also recommends that pathologists should note cases of pure desmoplastic melanoma (as opposed to the presence of desmoplasia admixed with spindle cell and/or epithelioid cells) as this may impact decisions about further diagnostics and treatment.[43]

Some melanocytic proliferations can be diagnostically challenging. Examples include atypical melanocytic proliferation, melanocytic tumor of uncertain malignant potential, superficial melanocytic tumor of uncertain significance, atypical Spitz tumor, and atypical cellular blue nevus. These lesions are more frequently seen in younger patients, and when suspected, referral to a pathologist with expertise in atypical melanocytic lesions is recommended. In cases where melanoma is included in the differential diagnosis, the pathology report should include prognostic elements as for melanoma.

Molecular Characterization of the Primary Tumor

Comparative genomic hybridization (CGH) or fluorescence in situ hybridization (FISH) may be helpful in detecting the presence of selected gene mutations for histologically equivocal lesions. CGH is a more comprehensive technique than FISH that may offer higher sensitivity and specificity in identifying relevant copy number changes, as suggested by a small study on atypical Spitz tumors.[47]

In addition to CGH and FISH, a number of diagnostic or prognostic genetic tests for melanoma are in development.[48-52] One of these commercially available gene expression profiling tests was developed to help predict the biologic behavior of atypical melanocytic lesions with indeterminate histopathology (eg, melanocytic or Spitz tumors of uncertain malignant potential).[50] Although there is a tremendous clinical need for this technology, the challenges of developing a truly discriminant test are substantial. Even in the presence of sentinel lymph node metastasis these indeterminate neoplasms can demonstrate a strikingly benign biologic behavior, making it exceedingly difficult to define a true positive (fully malignant lesion).[53-58] Furthermore, as the very few events in this low-risk group tend to be late, long-term follow-up is required to validate the prognostic significance of this test.

Another currently commercially available gene expression profiling test is being marketed to supplement prognostic information derived from the primary tumor and sentinel lymph nodes.[48,49] This technique was developed to discriminate patients at low risk versus high risk for metastatic disease based on the differential expression of 28 genes. The gene set was developed from a relatively high-risk training set of patients and tested in a different relatively high-risk validation set of patients. This gene expression profile has been validated as independently predictive of outcome when compared to AJCC stage or sentinel lymph node status.[48,49] This test has not been directly evaluated in the context of all known prognostic characteristics of localized melanoma.[59] Furthermore, its independent prognostic value

has yet to be confirmed in a large population of patients with average- to low-risk melanoma.

Gene expression profiling for melanoma could be an enormously valuable contribution to understanding the biology of the disease. However, the difficulty of embracing gene expression profiling as an independent predictor of outcome is illustrated by the inconsistency of results across studies aimed at defining the most predictive gene sets for melanoma.[49,51,60-62] Comparison of the gene signatures identified in these studies show minimal overlap in specific genes thought to be predictive of outcome. The identification and validation of a prognostic gene expression profile is a complicated multi-step and often multi-study process, and there are many ways in which specifics of study design and methodology can impact the end result.[63-66] The lack of overlap in gene signatures identified as prognostic for melanoma is likely due to substantial differences in study design and methodology. Efforts to develop gene expression profiling prognostic assays for other types of cancer have also resulted in limited or partial overlap in the "gene signature" identified by different studies.[67-70]

Pathology of Nodal and Regional Disease

Among patients with nodal metastases (stage III), the clinical nodal status (nonpalpable vs. palpable) and the number of metastatic nodes are the most important predictors of survival.[71,72] The AJCC staging system has recognized this difference in prognosis among patients with pathologic stage III melanoma.[14] For patients with a positive sentinel lymph node, prognostic factors include number of positive nodes, tumor burden in the sentinel node, primary tumor thickness, mitotic rate and ulceration, and patient age.[28,73-80] For patients with clinically positive nodes, prognostic factors include number of positive nodes, extranodal extension, primary tumor ulceration, and patient age.[28,81-86]

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.[41] The presence of microsatellites, clinically evident satellites, and/or regional intransit disease is all part of the biologic continuum of regional lymphatic involvement, and these are all associated with a prognosis similar to that of patients with clinically positive nodes. This is recognized in the staging system with the designation of stage IIIC.

Clinical Characterization of Metastatic Disease

Among patients with distant metastatic melanoma (stage IV), the site of metastases is the most significant predictor of outcome. The three risk categories recognized by the AJCC are skin, soft tissue, and remote nodes (M1a); visceral-pulmonary (M1b); and visceral-nonpulmonary (M1c).[14,27] Elevated lactate dehydrogenase (LDH), likely a surrogate for overall tumor burden, is also an independent predictor of poor outcome in patients with stage IV disease and has been incorporated into the AJCC staging system; patients with distant metastases to any site and elevated LDH are in the highest risk category (M1c).[71,87,88] The prognosis for patients with metastatic melanoma has dramatically improved with the emergence of several effective systemic therapies associated with improved overall survival (OS) and long-term survival in some patients (See *Systemic Therapy for Advanced Melanoma*). It is unclear whether the factors prognostic for outcome will also change.

Molecular Characterization of Metastatic Disease

Several targeted therapies have been developed for patients with melanoma harboring specific mutations (See *Systemic Therapy for Advanced Melanoma,* sub-sections *BRAF-targeted Therapies* and *Other Targeted Therapies*). Patients with metastatic melanoma with activating mutations of *BRAF*, an intracellular signaling kinase in the mitogen activated protein kinase (MAPK) pathway,[89-91] have been

shown to be likely to respond to BRAF inhibitors.[92-95] Likewise, patients with metastatic melanoma with activating mutations in *KIT*, a receptor tyrosine kinase, have been shown to be more likely to respond to imatinib, a tyrosine kinase inhibitor, compared with patients without activating *KIT* mutations.[96-98] A number of tests have been developed for detecting *BRAF* and *KIT* mutations common in metastatic melanoma. The sensitivity and accuracy of these tests vary, and improved assays are in development.[99-110] For both *BRAF* and *KIT* mutations, studies have investigated the intra- and inter-tumoral homogeneity, and found that mutation status can change during disease progression, such that recurrences or metastases may have mutations not present in the primary tumor.[111-115] Pathologists are now strongly encouraged to test for and report the presence or absence gene mutations (*BRAF*, *KIT*) that may impact treatment options in patients with metastatic melanoma.

Pathology Report: NCCN Recommendations

For the pathology report, the NCCN Melanoma Panel recommends at a minimum the inclusion of Breslow thickness, ulceration status, mitotic rate (#/mm^2), deep and peripheral margin status (positive or negative), presence or absence of microsatellites, pure desmoplasia if present, and Clark level for nonulcerated lesions 1.0 mm or less where mitotic rate is not determined. Ideally, mitotic rate should be reported for all lesions, as it is emerging as an independent predictor of outcome. When pure desmoplastic melanoma is suspected, multidisciplinary consultation including an experienced dermatopathologist is recommended for determining staging and treatment options.

The panel agreed that recording of additional parameters identified by the AAD task force would be helpful, but not mandatory. CGH or FISH should be considered to detect the presence of selected gene mutations for histologically equivocal lesions. While there is interest in newer prognostic molecular techniques such as gene expression profiling to help differentiate benign from malignant neoplasms, or to help distinguish melanomas at low- versus high-risk for metastasis, routine (baseline) genetic testing of primary cutaneous melanomas (before or following sentinel lymph node biopsy [SLNB]) is not recommended outside of a clinical study.

For stage III patients, the NCCN Melanoma Panel recommends reporting the number of positive nodes, the total number of nodes examined, and the presence or absence of extranodal tumor extension. In addition, the panel recommends recording the size and location of tumor present in a positive sentinel node.

For stage IV patients, the clinician is responsible for reporting the number and sites of metastatic disease. In addition to histologic confirmation of metastatic disease whenever possible, pathologists are now strongly encouraged to test for and report the presence or absence of gene mutations (*BRAF*, *KIT*) that may impact treatment options in patients with metastatic melanoma. Because these inhibitors of BRAF or KIT are recommended only for patients with advanced disease, *BRAF* and *c-KIT* mutational analyses are clinically useful only for patients with advanced disease considering these molecular targeted therapies. In the absence of metastatic disease, testing of the primary cutaneous melanoma for *BRAF* mutation is not recommended.

Preliminary Workup: NCCN Recommendations

After the diagnosis of cutaneous melanoma has been confirmed, detailed personal and family history, including any personal history of prior melanoma or dysplastic nevi, should be obtained. In the physical examination of patients with invasive melanoma, physicians should pay special attention to the locoregional area and lymph node drainage

basin(s) of the established melanoma. A complete dermatologic examination is recommended for all patients with newly-diagnosed melanoma.

Patients can be clinically staged after histopathologic microstaging of the primary tumor, and a complete history and physical examination (H&P) as described above. Patients are staged according to the AJCC criteria. Patients with in-situ melanoma are stage 0. Patients with invasive (not in-situ) melanoma and clinically negative nodes are stage I-II. The NCCN Guidelines have further stratified clinical stage I patients into three groups based on risk of lymph node involvement.

Patients with palpable regional nodes, as well as those with in-transit disease or microsatellites are clinical stage III.

Patients with distant metastases are clinical stage IV, and should be further assigned to a substage by recording all sites of metastatic disease and the serum LDH (within normal limits or elevated).

Based on preliminary workup and clinical staging patients are stratified into one of six groups for further workup and treatment:

- Stage 0 (melanoma in situ); or stage IA or IB with thickness 0.75 mm or less, regardless of other features (eg, ulceration, mitotic rate)
- Stage IA with thickness 0.76 to 1.0 mm, with no ulceration, and mitotic rate 0 per mm^2
- Stage IB with thickness 0.76 to 1.0 mm with ulceration or mitotic rate greater than or equal to 1 per mm^2; or stage IB or II with thickness 1.0 mm thick, any feature (eg, with or without ulceration, any mitotic rate), and clinically negative nodes
- Stage III with clinically detected (palpable) positive nodes, microscopic satellitosis (from assessment of the primary lesion), and/or in-transit disease
- Stage IV (distant metastatic disease)

Further Workup and Pathologic Staging

Laboratory Tests and Imaging

There are several reasons to embark on a further imaging and diagnostic workup to determine the extent of disease in the melanoma patient. One is to establish a set of baseline images against which to compare future studies in a patient at risk for relapse. Another is to detect clinically occult disease that would affect immediate treatment decisions. A third reason is to define homogeneously staged patients for inclusion into clinical trials. Although patients greatly value the negative result of a cross-sectional imaging study, physicians need to be cautious about over interpreting the significance of the findings, recognizing that all tests have relatively insensitive lower limits of resolution. Finally, any test carries the very real possibility of detecting findings unrelated to the melanoma, findings that can lead to morbid invasive biopsy procedures, or at the very least substantial patient anxiety while awaiting results of interval follow-up studies.

The yield of routine blood work and imaging studies in screening patients with clinical stage I-II melanoma for asymptomatic distant metastatic disease is very low. Screening blood tests are very insensitive, and the findings of cross-sectional imaging for patients with clinical stage I-II are often nonspecific, with frequent false-positive findings unrelated to melanoma.[116-118]

The yield of imaging studies has been more extensively evaluated in the context of patients with stage III melanoma. In patients with a positive

SLN, the yield of cross-sectional imaging in detecting clinically occult distant metastatic disease ranges from 0.5% to 3.7%.[119-122] True positive findings are most often found in patients with ulcerated thick primary tumors and a large tumor burden in their sentinel nodes. In asymptomatic patients with clinically positive nodes, the yield of routine cross-sectional imaging is a bit higher than in patients with positive sentinel nodes, reported at 4% to 16%.[123-125] All of these series also report a significant incidence of indeterminate or false-positive radiologic findings that are unrelated to the melanoma.

These retrospective studies report minimum estimates, as it is very difficult to define a study population of truly “imaging-naïve” high-risk stage II and stage III patients. It is probable that, among the entire denominator of stage III patients, some would have been defined as stage IV based on imaging before the study cohort was assembled. Furthermore, as a substantial proportion of clinical stage III patients will ultimately develop distant metastases,[126] the inability of cross-sectional imaging studies to detect metastatic disease at diagnosis of stage III is a relatively poor predictor of future events.

PET scanning has attracted interest as a means of enhancing detection of subclinical metastatic disease. Most investigators have described very low yield and poor sensitivity in detecting metastatic disease in patients with clinically localized melanoma.[127-130] In patients with stage III disease, PET/CT scan may be more useful. In particular, PET/CT scans can help to further characterize lesions found to be indeterminate on CT scan, and can image areas of the body not studied by the routine body CT scans (ie, arms and legs).[131,132] A systematic review of 17 diagnostic studies documented PET sensitivity ranging from 68% to 87% and specificity ranging from 92% to 98% for stage III and IV melanoma compared to sensitivity ranging from 0% to 67% and specificity ranging from 77% to 100% for stage I and II melanoma.[133]

Another large meta-analysis suggested that PET/CT was superior over CT in detecting distant metastases.[134] Other recent studies in patients with stage III or IV melanoma have reported similar results, and indicated that additional information provided by PET/CT may impact treatment decisions in up to 30% of patients, with the greatest impact seen in surgical management.[132,135]

Another consideration for baseline imaging is the impact on early detection of central nervous system (CNS) metastases. Early detection and treatment of subclinical CNS metastases is important because 1) clinically symptomatic CNS metastases are associated with significant morbidity and poor survival, and 2) outcomes after treatment are markedly better in patients with lower CNS tumor burden and/or asymptomatic metastases.[126,136-144] Although CNS recurrence is rare in patients who present with stage I-IIIB melanoma (≤5%), patients with stage IIIC disease have an appreciable risk (11%).[126] Although the yield of baseline CNS imaging may be low, it may be useful for comparison with follow-up scans in patients at risk of CNS recurrence.

Sentinel Lymph Node Biopsy

SLNB is a minimally invasive staging procedure developed to further risk-stratify patients with clinical stage I-II melanoma according to the presence or absence of subclinical nodal metastases. Patients with positive SLNB are at higher risk of recurrence, and might be candidates for complete lymph node dissection (CLND) and/or adjuvant systemic therapy.[145] The utility of SLNB for staging depends on a thorough understanding of 1) the technical aspects of the procedure that lead to successful identification and pathologic examination of a sentinel node; 2) the low rate of complications associated with the procedure; 3) the likelihood of sentinel node positivity; 4) the sensitivity of the test

(likelihood of false positives and false negatives); and 5) the prognostic significance of sentinel lymph node status.

Techniques of Sentinel Lymph Node Biopsy

SLNB is almost always performed at the time of initial wide excision; the validity of performing this technique after definitive wide excision has not been extensively studied. There is at least a theoretical concern that the relevant draining lymphatics could have been disturbed by the wide excision, especially if rotation flaps or skin grafts were used for reconstruction, degrading the accuracy of the SLNB procedure.

The technique for SLNB consists of preoperative dynamic lymphoscintigraphy, intraoperative identification using isosulfan blue or methylene blue dye, and a gamma probe to detect radiolabeled lymph nodes.[73,146-149] Many studies have reported high rates of successful sentinel lymph node detection using this robust technique (>95%).[19,73,146-149] SPECT scanning may enhance the accuracy of this technique in anatomically challenging regions, such as the head and neck, or when a faintly visible sentinel node might be otherwise overshadowed by the intense radioactivity at the primary injection site.[150,151]

Meticulous pathologic examination of all sentinel nodes is essential to maximize the probability of detecting all SLNs with microscopic disease. When micrometastases are not identified by routine hematoxylin and eosin (H&E) staining, serial sectioning and immunohistochemical staining (eg, with HMB-45 and/or Melan-A) has been shown to identify additional patients with positive sentinel nodes.[152-154] As the presence of even scattered clusters of melanoma cells in a sentinel node is clinically relevant, the AJCC was unable to determine a sentinel node tumor burden too low to report as metastatic disease.[27,155,156] On the other hand, the presence of bland or benign-appearing melanocytes should be interpreted with caution. These “nodal nevi” can masquerade as metastatic disease, when in fact long-term outcomes in patients with nodal nevi are similar to those of patients with negative SLNs.[157] When there is any doubt about the significance of abnormal melanocytes in a sentinel node, review by an experienced dermatopathologist is recommended.

Although the concept is simple, and the technical aspects of SLNB are very robust, with similar results reported from many centers around the world using innumerable variations of the basic technique, the successful identification and characterization of the sentinel node depends on dedicated and meticulous cooperation among nuclear medicine, surgery, and pathology.

Complications of Sentinel Lymph Node Biopsy

SLNB is associated with a low complication rate (5% in the Sunbelt Melanoma trial; 10% in MSLT-1).[158-165] Two prospective randomized trials have shown that the complication rate is significantly lower with SLNB compared with completion lymph node dissection.[158,159] The most common complications associated with SLNB are wound dehiscence and infection, seroma/hematoma, and lymphedema; other associated complications are nerve injury and thrombophlebitis, deep vein thrombosis, and hemorrhage.[158-160,162-167] Allergic reactions to the blue dye used in SLNB have also been reported.[159,161,162] Risk of complications, particularly lymphedema, is higher for SLNB of the groin compared with the axilla or neck [158,165,168]

Rates and Predictors of Sentinel Lymph Node Positivity

Depending on a variety of factors described below, 5% to 40% of patients undergoing SLNB will be upstaged from clinical stage I-II to pathologic stage III, based on subclinical micrometastatic disease in the SLN.[18,73,147-149,169-174] Multivariate analyses have identified factors

independently predictive of a positive SLN. The correlation between increased primary tumor thickness and SLN positivity is well established.[18,45,148,169,171,172,175-177] Due in part to the low probability of finding a positive sentinel node in patients with thin primary melanomas (≤1 mm), the utility of SLNB in this population is controversial and is discussed below in *SLNB in Thin (≤1 mm) Melanoma*.

In addition to Breslow thickness, other primary lesion characteristics (eg, Clark level, mitotic rate, ulceration, lymphovascular invasion, VGP, anatomic site, tumor infiltrating lymphocytes, regression) and patient characteristics (eg, sex, age) have been assessed for their association with SLN status in patients with primary melanomas thicker than 1 mm. For each of these factors, however, their prognostic value is unclear due to results varying between studies.[177-182] For example, results vary regarding the prognostic significance of patient age for predicting likelihood of SLN positivity, but most studies show higher risk of SLN involvement in younger patients.[18,45,148,171,175,176,183] An AJCC database analysis of patients with cutaneous melanoma, no clinically detectable LN metastases (n = 7756), and SLNB showed that age was an independent predictor of SLN positivity, with higher rates of SLN positivity in younger patients (<20 y), but that younger patients lived longer, nonetheless.[184] High age (>80 y) was associated with lower rates of SLN positivity, but nonetheless this group had lower survival rates. Analysis of a SEER database yielded similar results.[180]

MSLT-1: Prospective Randomized Trial on SLNB

MSLT-I, an international, multicenter, phase III trial, was initiated in 1994 to evaluate the impact of initial management with SLNB on the DSS of patients presenting with localized melanoma. Patients were treated by wide excision, followed by either SLNB (and immediate lymphadenectomy if SLN positive) or followed by observation of the nodal basin (and lymphadenectomy upon clinical detection of nodal metastasis). The final long-term results of this trial were recently reported, and provide the best available data regarding the utility of SLNB, as described in the following sections.[173]

Accuracy of Sentinel Lymph Node Biopsy

Both retrospective analyses and data from MSLT-I have been evaluated to determine the false negative rate of SLNB, or the probability of missing a positive sentinel node if present. The false-negative rate is strictly defined as the number of patients with nodal recurrences after negative SLNB (false negatives), divided by the total number of patients with nodal involvement, including false negatives and patients with a positive SLNB (true positives). Using this definition, MSLT-I and retrospective series have reported false-negative rates of up to 20%.[73,147,149,170,173,174,182,185]

Prognostic Value of the Sentinel Node

Retrospective analyses have indicated that among patients with clinically node negative localized melanoma undergoing SLNB, the status of the sentinel node is the most important prognostic factor, both for disease progression and DSS.[71,73,172,182,185,186] Primary tumor thickness is also an independent predictor of progression and survival;[71] however, and one study has shown that the prognostic value of SLN positivity is greater for patients with tumor thickness >1 mm.[187] The prognostic value of SLN status in patients with thin primary melanomas is discussed further in the next section.

Prospective data from MSLT-I confirm the prognostic value of SLN status in patients with primary tumors ≥1.2 mm thick; among patients screened with SLNB, DSS was significantly worse in those with versus without sentinel node involvement.[173] Sentinel lymph node status was also the strongest predictor of disease-free survival (DFS) by multivariate analysis.

Among patients with SLN positivity, the SLN burden (number of positive SLNs, size and location of tumor in the SLN[s]) is prognostic for recurrence and survival.[74-80]

Therapeutic Value of SLNB

SLNB has limited therapeutic value. Although MSLT-1 largely confirmed the known role of SLNB as a very important staging test, SLNB did not improve DSS compared with nodal basin observation, regardless of primary lesion thickness. SLNB did improve DFS by 7% and 10% for patients with intermediate thickness (1.2–3.5 mm) or thick (>3.5 mm) primary lesions, respectively. Improvements in DFS were due in large part to the higher rate of nodal relapse in the nodal basin observation group.

In a prespecified retrospective subset analysis of patients who developed nodal metastases from intermediate-thickness (1.2–3.5 mm) melanoma, MSLT-I confirmed a survival advantage to those with microscopic versus macroscopic disease at the time of detection and removal (10-year DSS for those detected by SLNB versus nodal basin observation: 62% vs. 41.5%, $P = .006$). A similar survival advantage was not seen in patients with thick (>3.5 mm) melanomas and positive nodes.

In summary, although SLNB improved survival for the subgroup of patients having both intermediate thickness primary lesions and lymph node involvement, the study population as a whole did not benefit because SLNB did not improve survival in other subgroups (patients with thick primary lesions and/or who did not develop lymph node metastasis).

The therapeutic value of SLNB for patients with thin melanomas (1.2 mm or less) was not specifically addressed in the MSLT-I trial.

Utility of SLNB in Patients with Unusual Presentations

SLNB in Thin (≤1 mm) Melanoma

Among patients with thin melanoma selected for SLNB, rates of SLN positivity are low, around 5% in most studies (Table 1). Primary tumor thickness is the single factor that most consistently predicts SLN positivity (Table 2), in large part because other high-risk features such as ulceration and high mitotic rate are seen so infrequently. A review by Andtbacka and Gershenwald[188] reported an overall SLN metastasis rate of 2.7% in patients with melanoma thinner than 0.75 mm. In patients with melanoma 0.75 to 1.0 mm thick, 6.2% of patients selected to undergo SLNB were found to have a positive SLN.

Other than thickness, individual studies have inconsistently identified additional factors to be predictive of a positive SLN among patients with thin melanoma.[188] These include Clark level, mitotic rate, ulceration, lymphovascular invasion, VGP, and TIL.[16,17,19,45,71,186,189-198] For thin melanomas the significance of tumor regression as a predictor is controversial, though most studies have reported no association.[17,191,192,195,199]

One multi-institutional review of 1250 patients with thin melanomas (≤1 mm) found that less than 5% of melanomas thinner than 0.75 mm had positive SLNs regardless of Clark level and ulceration status.[190]

However, another review found that for patients with thin melanomas and at least one risk factor (ulceration, Clark level IV, nodular growth, mitosis, regression, or age ≤40 years), the SLN positivity rate was as high as 18%.[200]

In patients with thin melanoma the prognostic value of SLNB results is unclear. A number of studies have associated SLN positivity with worse

disease-free or melanoma-specific survival in patients with thin primary melanomas,[186,191,201] while others have reported no association.[192,193]

Table 1. Rate of Positive SLN in Thin Melanomas (≤1 mm)

Study	Total Patients	Positive SLN	
	N	n	%
Statius Muller 2001[147]	104	7	6.7%
Rousseau 2003[148]	388	16	4.1%
Bleicher 2003[202]	272	8	2.9%
Olah 2003[149]	89	12	13%
Oliveira 2003[16]	77	6	7.8%
Borgognoni 2004[170]	114	2	1.8%
Stitzenberg 2004[195]	146	6	4.1%
Sondak 2004[18]	42	4	9.5%
Puleo 2005[196]	409	20	4.9%
Kruper 2006[171]	251	13	5.2%
Ranieri 2006[191]	184	12	6.5%
Cascinelli 2006[172]	145	6	4.1%
Nowecki 2006[174]	260	17	6.5%
Wong 2006[192]	223	8	3.6%
Wright 2008[186]	631	31	5.0%
Murali 2012[193]	432	29	6.7%
Mozzillo 2013[201]	492	24	4.9%
Venna 2013[189]	450	34	7.6%
Cooper 2013[203]	189	3	1.6%
Total	**4898**	**258**	**5.3%**

SLN, sentinel lymph node

Table 2. Effect of Thickness on Rate of Positive SLN in Thin Melanomas (≤1 mm)

	Primary Tumor Thickness			
	<0.75 mm		0.75–1.0 mm	
	Positive SLN		Positive SLN	
Study	n/N	%	n/N	%
Bleicher 2003[202]	2/118	1.7%	6/154	3.9%
Kesmodel 2005[19]	1/91[a]	1.1%	8/90[a]	8.9%
Puleo 2005[196]			20/409	4.9%
Ranieri 2006[191]	2/86	2.3%	10/98	10.2%
Wong 2006[192]	0/73	0%	8/150	5.3%
Wright 2008[186]	16/372	4.3%	15/259	5.8%
Vermeeren 2010[204]	0/39[b]	0%	5/39[b]	12.8%
Murali 2012[193]	3/113	2.7%	26/290	9.0%
Venna 2013[189]	7/170[c]	4.1%	27/280[c]	9.6%
Total	**31/1062**	**2.9%**	**125/1769**	**7.1%**

SLN, sentinel lymph node
[a]Subgroups were primary tumor thickness <0.76 mm, 0.76–1.0 mm; all had VGP
[b]Subgroups were primary tumor thickness ≤0.75 mm, 0.76–1.0 mm
[c]Subgroups were primary tumor thickness <0.8 mm, ≥0.8 mm

SLNB in Desmoplastic Melanoma

Although estimates vary across studies, rates of SLN positivity tend to be lower with pure desmoplastic melanoma compared with mixed desmoplastic or other types of melanoma.[205-214] Moreover, several studies have shown that among patients with desmoplastic melanoma, SLN positivity does not consistently correlate with DSS.[209,211,214] Variability in results may be due in part to lack of standardized criteria for defining pure desmoplastic melanoma.[215-218] Assignment may vary between pathologists and across institutions. In the setting of these conflicting reports, the role of SLNB in patients with pure desmoplastic melanoma remains controversial.

Biopsy of Palpable Lymph Nodes

Fine-needle aspiration (FNA), with or without ultrasound guidance, has been shown to have high sensitivity and specificity for detecting melanoma in enlarged lymph nodes (detected clinically or by imaging).[219-221]

Full Workup and Pathologic Staging: NCCN Recommendations

Practices among the NCCN Member Institutions vary greatly with respect to the appropriate workup of a melanoma patient. In the absence of compelling data beyond the retrospective series cited above, for the most part, recommendation for the appropriate extent of workup is based on non-uniform consensus within the panel.

Stage 0, I, and II

Workup

The panel stressed the importance of a careful physical examination of the primary site, the regional lymphatic pathways and lymph node basin, and the remainder of the skin. Although nodal basin ultrasound is not a substitute for SLNB, the procedure should be considered for patients with an equivocal regional lymph node physical exam prior to SLNB. Abnormalities or suspicious lesions on nodal basin ultrasound should be confirmed histologically.

Routine cross-sectional imaging (CT, PET/CT, or MRI) is not recommended for these patients. Despite the very low yield of cross-sectional imaging, there was increasing disagreement about what consensus-based recommendations should be made for clinically node negative patients at the higher risk end of the spectrum. There was uniform consensus that imaging studies were indicated to investigate specific signs or symptoms. Routine blood tests are not recommended for patients with melanoma in situ or stage I and II disease.

Sentinel Lymph Node Biopsy

The NCCN Melanoma Panel does not recommend SLNB for patients with in situ melanoma (stage 0). The panel discussed at length the lower limit of probability of sentinel node positivity that should prompt a discussion of SLNB for stage I melanoma. According to data discussed above, Breslow thickness is the main factor associated with SLN positivity.

In general, the panel does not recommend SLNB for stage IA or IB lesions that are very thin (≤0.75 mm) unless there is considerable uncertainty about the adequacy of microstaging. Conventional risk factors such as ulceration, high mitotic rate, and lymphovascular invasion are very uncommon in melanomas 0.75 mm thick or less. In the rare event that a conventional high-risk feature is present, the decision about SLNB should be left to the patient and the treating physician. For patients with stage IA melanomas that are 0.76 to 1.0 mm thick without ulceration, and with mitotic rate 0 per mm^2, SLNB should be considered in the appropriate clinical context.

SLNB should generally be discussed and offered for patients with higher-risk stage IB (>1 mm thick or 0.76–1.0 mm thick with ulceration or mitotic rate ≥1 per mm^2) or stage II melanoma.

Any discussion of the SLNB procedure in patients with stage I or II melanoma should reflect what is known about the prognostic value of SLNB on various clinical endpoints, its defined accuracy and false negative rate, the potential morbidity of the procedure, and what (if anything) will be done differently once the SLN status is known.

Meticulous pathologic examination of all sentinel nodes is mandatory. When micrometastases are not identified by routine H&E staining, serial sectioning and immunohistochemical staining should be performed.

There is no sentinel node tumor burden too low to report as metastatic disease, including even scattered clusters of melanoma cells. On the other hand, the presence of bland or benign-appearing melanocytes should be interpreted with caution. When any doubt is present, review by an experienced dermatopathologist is recommended.

In patients who otherwise would be candidates for SLNB, the decision to not perform SLNB may be based on significant patient comorbidities or individual patient preference. There is controversy regarding the diagnostic criteria for, the probability of a positive sentinel node in, and the prognostic significance of the sentinel node in pure desmoplastic melanoma. Clinicians may consider forgoing SLNB on confirmed pure desmoplastic melanoma. Multidisciplinary consultation including a dermatopathologist is recommended for determining staging and treatment options.

The validity of SLNB in accurately staging patients after prior wide excision is unknown. As such, wide excision before planned SLNB is discouraged, although patients may be considered for the procedure on an individual basis if they present for that discussion after initial wide excision.

The panel discussed the appropriate management of clinically negative lymph nodes in patients at risk for regional metastases, in the event that SLNB is unavailable. Based on the results of three prospective randomized trials, the panel does not recommend routine elective lymph node dissection for this group. Wide excision alone or referral to a center where lymphatic mapping is available are both acceptable options in this situation. While nodal basin ultrasound surveillance would seem to be another reasonable option in this setting, its value has not been defined in prospective studies.

Stage III Workup

Stage III Sentinel Node Positive

Most panel members acknowledged the low yield of screening CT or PET/CT scans in patients with a positive sentinel lymph node. Based on the results of the studies reported in the literature and the absence of conclusive data, there was consensus that cross-sectional imaging could be considered at baseline for staging (category 2B) or to assess specific signs or symptoms (category 2A).

Stage III with Clinically Positive Node(s)

For patients presenting with clinical stage III disease who have clinically positive node(s), all panel members believe it is appropriate to confirm the suspicion of regional metastatic disease, preferably with FNA, or with core, incisional, or excisional biopsy of the clinically enlarged lymph node. If FNA is non-diagnostic in the setting of high clinical suspicion, excisional biopsy, planned with therapeutic lymph node dissection (TLND) in mind, is appropriate. Clearly, in patients without an antecedent history of melanoma, this would have been the initial diagnostic test. At a minimum, a pelvic CT scan is recommended in the setting of inguinofemoral lymphadenopathy to rule out associated pelvic or retroperitoneal lymphadenopathy. Most of the panel also endorsed baseline cross-sectional imaging for staging purposes and to evaluate specific signs or symptoms.

Stage III In-transit

For the small group of patients presenting with stage III microsatellitosis or in-transit disease, the workup outlined above for clinical stage III nodal disease, including histologic confirmation of the in-transit metastasis, and cross-sectional imaging, is appropriate.

SLNB may be considered for patients with resectable solitary in-transit stage III disease (category 2B recommendation). However, while SLNB

may be a useful staging tool, its impact on the OS of these patients remains unclear. Likewise for patients with microsatellitosis, while SLN positivity would upstage the disease to N3, stage IIIC, its significance in treatment decisions has not been clearly defined.

Since patients with stage IIIC have an appreciable risk of symptomatic CNS recurrence, and symptomatic CNS metastasis are associated with significant morbidity and poor survival, baseline CNS imaging should be considered in these high-risk patients.

Stage IV Workup

For patients presenting with stage IV distant metastatic disease, all panel members agree it is appropriate to confirm the suspicion of metastatic disease with either FNA or core, incisional, or excisional biopsy of the metastases. Genetic analyses (eg, *BRAF* or *KIT* mutation status) are appropriate for patients being considered for treatment with targeted therapy, or if mutational status is relevant to eligibility for participation in a clinical trial. To ensure that adequate metastatic material is available for mutational analysis, biopsy (core, excisional, or incisional) is preferred if initial therapy is to be systemic and archival tissue is not available. However, the panel also recognized that brain metastases are typically treated without histologic confirmation.

Panelists encourage baseline chest/abdominal/pelvic CT with or without PET/CT in patients with stage IV melanoma. Because patients with metastatic melanoma have a high incidence of brain metastases, brain MRI or CT scan with contrast should be performed at presentation with stage IV disease. Brain MRI is also recommended if patients have even minimal symptoms or physical findings suggestive of CNS involvement, or if results of imaging would affect decisions about treatment.

Although LDH is not a sensitive marker for detecting metastatic disease, the panel recognizes its prognostic value. It is recommended that serum LDH be obtained at diagnosis of stage IV disease. Other blood work may be done at the discretion of the treating physician.

Treatment of Primary Melanoma

Wide Excision

Surgical excision is the primary treatment for melanoma. Several prospective randomized trials have been conducted in an effort to define optimal surgical margins for primary melanoma (Table 3).

In an international prospective study carried out by WHO, 612 patients with primary melanomas not thicker than 2.0 mm were randomized to wide excision with 1 cm or ≥3 cm margins.[222,223] At a median follow-up of 90 months, local recurrence, DFS and OS rates were similar in both groups. Similarly, Swedish and French randomized trials confirmed that survival was not compromised by narrower margins in melanomas thinner than 2 mm.[224,225]

A multicenter European trial randomized 936 patients with melanoma thicker than 2.0 mm to wide excision with 2 or 4 cm margins.[226] The 5-year OS rate was similar in the two groups. This is in keeping with previous trials that found no survival benefits with margins wider than 2 cm for thicker lesions.[227,228] A systematic review and meta-analysis of the first three trials shown in Table 3 reported that surgical excision margins of at least 1 cm and no more than 2 cm are adequate.[229]

A recent update on the UK-based prospective trial of 1- versus 3-cm margins in patients with melanomas greater than 2 mm thick showed that at a median follow-up of 8.8 years, wider margin was associated with statistically significantly improved melanoma-specific survival (see Table 3 footnote).[230] OS was not significantly different between the

treatment groups. Although this is the only prospective trial that has shown a wider margin to be associated with a survival advantage, this is not practice-changing finding. The current recommendations are for 2-cm margins in this population, and this trial did not demonstrate superiority of 3-cm over 2-cm margins.

Recent large retrospective analyses are generally supportive of the margin recommendations that were based on prospective randomized trials.[231-236]

Table 3. Studies That Evaluated Surgical Margins of Wide Excision of Melanoma

Study	Year	N	Follow-up (years)	Thickness (mm)	Margin (cm)	LR	OS
WHO[222,223]	1991	612	8	≤2	1 vs. ≥3	NS	NS
Sweden[224]	2000	989	11	>0.8–2.0	2 vs. 5	NS	NS
Intergroup[227]	2001	468	10	1–4	2 vs. 4	NS	NS
France[225]	2003	326	16	≤2	2 vs. 5	NS	NS
UK[230,237]	2016	900	8.8	>2	1 vs. 3	NS	NS[a]
Sweden[226]	2011	936	6.7	>2	2 vs. 4	NS	NS

LR, local recurrence; OS, overall survival; NS, non-significant
[a]Analysis after a median follow-up of 5.7 years showed no significant difference in overall survival or melanoma-specific survival, but analysis after a median follow-up of 8.8 years showed significantly better melanoma-specific survival for patients with 3-cm vs. 1-cm excision margins (unadjusted HR 1.24 [95% CI 1.01–1.53]; *P* = .041) but no significant improvement in overall survival (unadjusted HR 1.14 [95% CI, 0.96–1.36]; *P* = .14).

Management of lentigo maligna and in situ melanoma may present unique problems because of the characteristic, yet unpredictable, subclinical extension of atypical junctional melanocytic hyperplasia, which may extend several centimeters beyond the visible margins.[238-240] In a prospective study of 1,120 patients with melanoma in situ treated by Mohs surgery, 9-mm surgical margins resulted in removal of 99% of melanomas while 6-mm margins removed 86%.[241] Retrospective analyses have also shown that >5 mm margins are often needed for complete histologic clearance of melanoma in situ, particularly for the lentigo maligna subtype.[240,242-244] Mohs micrographic surgery or staged excision with or without immunohistochemical staining aimed at complete surgical excision with meticulous margin control have demonstrated high local control rates in lentigo maligna.[245-247]

Alternatives to Excision: Topical Imiquimod or Radiation

Although surgical excision remains the standard of care for in situ melanoma, it is sometimes not feasible due to comorbidity or cosmetically sensitive tumor location. Topical imiquimod has emerged as a treatment option, especially for lentigo maligna.[248-264] Topical imiquimod was associated with high rates of clinical and histologic clearance (70%–100%) and low recurrence rates (0%–4%) in most studies, whether used as first-line treatment (as monotherapy or prior to excision) or second-line treatment for incompletely excised lentigo maligna, or adjuvant therapy for lesions excised with narrow margins. However, long-term, comparative studies are still needed.

Radiotherapy has also been used selectively for lentigo maligna. In a systematic review of retrospective studies reporting outcomes for patients with lentigo maligna treated with definitive primary RT, there were 18 recurrences in a total of 349 assessable patients (5%), after a median follow-up of 3 years, and disease progressed to lentigo maligna melanoma in 5 cases (1.4%).[265] There were 8 in-field recurrences (5 lentigo maligna, 3 lentigo maligna melanoma) out of 171 assessable patients (4.7%), and 5 marginal recurrences out of 123 assessable patients (4.1%). The retrospective studies used a variety of radiation protocols, including superficial RT and Grenz rays, but there were no

clear trends to indicate the optimal approach. Another large retrospective study (not included in the aforementioned meta-analysis) tested Grenz ray radiation in a mixed population of patients with lentigo maligna and early lentigo maligna melanoma.[266] Complete clearance without relapse was observed in 83% of 350 patients who received RT as primary therapy, and in 90% of 71 patients who received RT after partial excision.

Since tumor border delineation for lentigo maligna is smaller on clinical exam than with Wood lamp or digital epiluminescence microscopy, collaboration with a dermatologist who can perform these procedures is necessary to help prevent these marginal failures.[267]

NCCN Recommendations

The clinical/surgical margins discussed below refer to those taken at the time of surgery and do not necessarily correlate with gross pathologic/histologic margins measured by pathologists.

For in situ melanoma, a measured margin of 0.5 to 1 cm around the visible lesion should be obtained. For large in situ lentigo maligna melanoma, surgical margins greater than 0.5 cm may be necessary to achieve histologically negative margins. In the absence of prospective clinical trials testing margins for standard excision, this margin range is recommended based on panel consensus, data from retrospective studies, and results from the large prospective study described above that showed that increasing Mohs microsurgery margins from 6 mm to 9 mm significantly improved the rate of complete histologic clearance. More exhaustive histologic assessment of margins such as staged excision for lentigo maligna melanoma should be considered. For selected patients with positive margins after optimal surgery, topical imiquimod or RT can be considered as non-standard options (category 2B).

For melanomas 1.0 mm or less, wide excision with a 1-cm margin is recommended (category 1). Wide excision with a 1- to 2-cm margin is recommended for melanomas measuring 1.01 to 2 mm in thickness (category 1). For melanomas measuring more than 2 mm in thickness, wide excision with 2-cm margins is recommended (category 1). Surgical margins may be modified to accommodate individual anatomic or cosmetic considerations. The panel recognized that 1- to 2-cm margins might be acceptable in anatomically difficult areas where a full 2-cm margin would be difficult to achieve.

Lymph Node Dissection

Completion Lymph Node Dissection After Positive SLNB

Traditionally, all patients with a positive SLNB have been advised to proceed to CLND. This is in part an extension of the observation that, in historical prospective trials, among patients with a positive node, survival was better in those patients where the node was removed when clinically occult by elective lymph node dissection rather than when clinically apparent by TLND.[268] There are a number of other theoretical reasons for recommending CLND to this patient population. These include the known probability of residual positive non-sentinel lymph nodes (NSLNs), the prognostic value of additional positive NSLNs, improved regional nodal basin control after CLND, the lower morbidity of CLND rather than TLND, and the potential to improve long-term DSS by early aggressive nodal basin intervention. Arguments against CLND include the cost and morbidity of the procedure,[269-274] and the fact that the procedure has never been demonstrated to offer clinical benefit to this group of patients, a group already defined as at increased risk of systemic disease based on the presence of their positive SLNB. Over the last 25 years, much has been learned about the natural history of patients with a positive sentinel node to inform many of the points cited above. More importantly, two pivotal prospective randomized trials have

been conducted to directly address the impact of CLND on a number of these clinical endpoints.[275,276]

Likelihood of Non-Sentinel Lymph Node Positivity

Among patients with a positive sentinel node, published studies have revealed additional positive non-sentinel nodes in approximately 20% of the CLND specimens (Table 4). Factors most predictive of additional non-sentinel node involvement include the largest size of the SLN metastasis,[77,79,172,277-289] the number of SLNs involved,[79,155,278,283,290] the distribution of metastasis in the SLN (subcapsular vs. parenchymal),[172,291,292] and primary tumor characteristics of thickness[277,278,281,285-288,293,294] and ulceration.[155,281,283,293,294] Several scoring systems have been developed to predict the likelihood of positive non-sentinel nodes based on SLN biopsy findings, primary tumor, and patient characteristics,[288,295-299] although the utility of each of these systems has been debated based on subsequent analyses.[80,281,283,300,301]

Table 4. Rates of Positive Non-Sentinel Lymph Nodes

Study	Patients with CLND, n	Patients with Positive NSLN, n (%)
McMasters 2002 [302]	272	45 (16%)
Dewar 2004[291]	146	24 (16%)
Sabel 2005[278]	221	34 (15%)
Kettlewell 2006[303]	105	34 (32%)
Cascinelli 2006[172]	176	33 (19%)
Govindarajan 2007[279]	127	20 (16%)
Gershenwald 2008[288]	343	48 (16%)
Cadili 2010[77]	606	142 (24%)
Leung 2013[293]	329	79 (24%)
Wevers 2013[295]	130	30 (23%)
Pasquali 2014[304]	1,538	353 (23%)
Bertolli 2015[285]	146	23 (16%)
Rutkowski 2015[287]	473	132 (28%)
Kim 2015[79]	111	13 (12%)
Total	**4723**	**1010 (21%)**

CLND, complete lymph node dissection; NSLN, non-sentinel lymph node

Prognostic Value of Complete Lymph Node Dissection

A number of retrospective studies have evaluated the prognostic value of NSLN involvement in patients who had a CLND after a positive SLN (no palpable lymph nodes). Compared to those without NSLN involvement detected by CLND, those with positive NSLN(s) have higher rates of recurrence[80,273,293] and poorer DFS,[305] melanoma-specific survival, and OS.[80,172,287,293,304-306] In fact, in the studies that evaluated the clinical importance of NSLN positivity by multivariate analysis, it was consistently one of the most important independent predictor of DSS.[273,293,304-306] Other factors identified to be independently associated with recurrence and survival include the number of positive

NSLNs[81,273,287] as well as the non-CLND factors of the primary tumor (site,[273] Breslow thickness,[80,287,301] and ulceration[80,273,287]), the nodal basin involved,[273] and the SLN burden (number of positive SLNs, size and location of tumor in the SLN[s]).[77,79,80,301]

The challenge of using the probability of NSLN positivity as a rationale to proceed to CLND is that patients with a positive NSLN are at much higher risk for distant metastases. This is a population that intuitively may be much less likely to benefit from additional treatment of the regional nodal basin.

Therapeutic Value of CLND

The impact of completion lymph node dissection on regional control and survival in the setting of a positive SLN has not been clearly demonstrated. Results from a few retrospective studies in patients with positive SLNB have shown that treatment with CLND versus observation may be associated with improved recurrence-free survival, but is not significantly associated with improved OS or melanoma-specific survival.[307-309] Two ongoing trials are designed to assess the therapeutic value of CLND for patients with positive sentinel lymph nodes (but no palpable nodes).

DeCOG-SLT is a phase III prospective randomized trial (https://clinicaltrials.gov/ct2/show/record/NCT02434107) in which melanoma patients with a positive SLNB were randomized to undergo immediate CLND (n = 241) or observation with nodal basin ultrasound surveillance (n = 242). At a mean follow-up of 34 months, CLND was not associated with any improvement in recurrence-free survival, distant-metastasis-free survival, or melanoma-specific survival.[275] An interesting subset analysis in this trial suggested that CLND was not associated with clinical benefit in patients with either high or low SLN tumor burden.

MSLT-II is a much larger international prospective randomized trial in which patients with a positive SLNB were randomized to undergo either immediate completion lymph node dissection or nodal basin ultrasound surveillance (clinicaltrials.gov/show/NCT00297895). This trial, which has completed accrual, should further clarify the issue of whether CLND has an impact on outcome.

Therapeutic Lymph Node Dissection

In patients with clinically involved lymph nodes but no distant disease, TLND is associated with 5-year survival rates of 30% to 50%, depending on number of lymph nodes involved, extracapsular extension, and high-risk features of the primary tumor (Breslow thickness, ulceration, site).[71,81,82,310-317] At present, there is no non-surgical therapy that has been shown to provide similar results (for survival).

Palliative Lymph Node Dissection

On occasion, lymph node dissection may be indicated for patients with distant metastatic disease in order to achieve regional nodal basin control.

Elective Pelvic Lymph Node Dissection

Among patients with positive inguinofemoral nodes and no clinical or radiologic evidence of positive pelvic nodes, there is some controversy as to the role of elective ileo-obturator lymph node dissection.[310,318-321] In these patients, the probability of clinically occult positive pelvic nodes is increased when there are clinically positive inguinofemoral nodes, three or more inguinofemoral nodes involved, or when Cloquet's node is positive.[322-327] Again, the impact of elective pelvic lymphadenectomy on survival in this specific patient cohort is unknown.[328]

Morbidity of Lymph Node Dissection

The value CLND for providing prognostic information and regional control must be weighed against morbidity of the procedure. Many studies have reported complication rates for between 40% to 60%,[269,329] but others have reported lower rates, between 20% to 40%.[158,159,271] Potential complications associated with CLND include wound dehiscence or infection, hematoma/seroma, neuropathy, lymphocele formation, and lymphedema.[158,159,269-272,311,317,329-331] Lymphedema and neuropathy can be persistent postoperative problems.[270-272,331] Most studies report lymphoedema rates between 20% to 30%, but some studies have reported lymphedema in up to 50% of patients.[86,269,271,272,331] Risk factors for complications during or after lymph node dissection include obesity and increased age.[331,332] The risk and severity of complications may depend on the location of the nodal basin undergoing lymph node dissection, with the groin being the highest risk location, especially for lymphedema.[158,271,274,317,331]

Technical Aspects of Lymph Node Dissection

CLND consists of an anatomically thorough dissection of the involved nodal basin. The extent of lymph node dissection is often modified according to the anatomic area of lymphadenopathy. There is some controversy on how best to define an adequate lymph node dissection. One measure of the completeness of a regional lymph node dissection is the number of lymph nodes examined. There is not uniform agreement on the number of lymph nodes needed to define an optimal CLND in a given lymph node basin.

It is unknown whether the extent of lymph node dissection can safely be modified according to the indication for the lymph node dissection (CLND due to positive sentinel lymph node, TLND for palpable lymph node(s), palliative lymph node dissection regional control in patients with distant metastatic disease) to limit the morbidity of the procedure. A number of investigators have attempted to evaluate this issue.[269,284,333-338]

NCCN Recommendations

If the sentinel node is negative, regional lymph node dissection is not indicated. For patients with stage III disease based on a positive SLN, a CLND of the involved nodal basin should be discussed and offered, in the context of all of the points raised above, including the probability of a positive NSLN, the prognostic value of the NSLN status, the morbidity of the procedure, and the fact that one prospective randomized controlled trial has shown no benefit in any clinically relevant endpoint. The impact of CLND on plans for adjuvant therapy or clinical trial enrollment should also be considered.

Patients presenting with clinically positive nodes without radiologic evidence of distant metastases should undergo wide excision of the primary site (if present) and CLND of the involved nodal basin. In the setting of inguinal lymphadenopathy, a pelvic dissection is recommended if the PET/CT or pelvic CT scan reveals iliac and/or obturator lymph node involvement (category 2A) or if a positive Cloquet's lymph node is found on intraoperative frozen section (category 2B). Pelvic dissection also should be considered for clinically positive inguinal-femoral nodes or if three or more inguinofemoral nodes are involved (category 2B). For primary lesions in the head and neck with clinically or microscopically positive lymph nodes in the parotid gland, a superficial parotidectomy alone is insufficient and the panel recommends appropriate neck dissection of the draining nodal basins.[339]

However, the NCCN panel felt that available retrospective evidence to date was insufficient to mandate that a specific number of nodes be

required to deem a lymph node dissection adequate for any designated lymph node basin. As a measure of quality control to ensure adequacy of lymphadenectomy, the committee recommended that the operative note fully describe the anatomic boundaries of the lymph node dissection.

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 described below, a large body of clinical evidence has amassed. Results from recent and ongoing trials support two 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.[340,341] Prospective clinical trials are evaluating targeted therapies as well as regimens combining multiple types of therapy (eg, IFN, chemotherapy, immune checkpoint inhibitors, targeted therapies) for use as adjuvant treatment for melanoma.[342-357]

Low-Dose and Intermediate-Dose Interferon

Low-dose adjuvant IFN typically has been administered subcutaneously at 3 MU/d for 3 d/wk. Various intervals and durations of low-dose IFN have been compared with observation in patients with fully resected non-metastatic melanoma at high-risk for recurrence (Table 5). 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 5). Intermediate-dose IFN, defined as 5 to 10 MU/d subcutaneously (SC) for 3 to 5 d/wk, 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 5).

Table 5. Low-Dose or Intermediate-Dose Adjuvant Interferon

Trial[a]	References	IFN Dose[b]	IFN type	Patients, n		Statistically Significant Impact of IFN	
				IFN	Obs	Relapse-free Survival[c]	Survival[d]
Italian Skin Cancer Foundation[e]	Rusciani 1997[358]	Low	2b	84	70	Yes; $P < .0001$[f]	No
Austrian Malignant Melanoma Group	Pehamberger 1998[359]	Low[g]	2a	143	150	Yes; $P = .02$	No
French Cooperative Group on Melanoma	Grob 1998[360]	Low	2a	244	243	Yes; $P = .035$	Trend: $P = .059$
Scottish Melanoma Group Study	Cameron 2001[361]	Low	2b	49	47	Overall: No 2-y rate: Yes; $P < .05$	No
WHO Melanoma Programme	Cascinelli 2001[362]	Low	2a	225	219	No	No
AIM HIGH – UK Coordinating Committee on Cancer Research	Hancock 2004[363]	Low	2a	338	336	No	No
EORTC 18871 and DKG-80-1	Kleeberg 2004[364]	Very low	2b	240	244	No	No
ECOG 1690	Kirkwood 2000[365] Kirkwood 2004[366]	Low	2b	215	212	No	No
EORTC 18952	Eggermont 2016[367]	Intermediate	2b	1109	279	No[h]	No[h]
DeCOG trial	Garbe 2008[368]	Low	2a	148	148	Yes; $P = .018$	Yes; $P = .005$
Nordic IFN trial	Hansson 2011[369]	Intermediate	2b	571	284	Yes; $P = .034$[i]	No

IFN, interferon; NR, not reported; Obs, observation

[a]All prospective, randomized, multicenter studies comparing adjuvant interferon with observation in patients with fully resected non-metastatic cutaneus melanoma at high-risk for recurrence.

[b]Low-dose IFN regimen: 3 MU SC 3 x/wk, for various intervals and durations; very-low-dose IFN regimen: 1 MU SC every other day; intermediate-dose IFN regimens: 10 MU SC 3–5 x/wk for 4 weeks, then 5–10 MU SC 3 x/wk.

[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 3 x/wk.

[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 non-ulcerated primary tumor.

High-Dose Interferon and Pegylated Interferon

High-dose IFN generally includes one month of IV induction with 20 MU/m^2/d for 5 d/wk followed by 11 months of intermediate-dose subcutaneous maintenance IFN with 10 MU/m^2/d for 3 d/wk. This regimen has been evaluated in five large prospective randomized clinical trials in patients with fully resected non-metastatic melanoma at high risk for recurrence (Table 6). The 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 and sometimes OS, at least at early time-points. However, both of these effects appear to diminish with longer-follow-up (Table 6). 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 5 and 6).[365]

In an attempt to reduce toxicities associated with adjuvant high-dose IFN, randomized trials have compared different dose schedules and durations.[370-375] 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 µg/kg SC per week for 8 weeks followed by maintenance with 3 µg/kg SC per week for an intended duration of five years.[376] Pegylated IFN improved recurrence-free survival compared with observation (4-year recurrence-free survival: 45.6% vs. 38.9%, P = .01); however, there was no statistically significant effect on OS. Based on these data, pegylated IFN alfa received approval by the U.S. Food and Drug Administration (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%; HR, 0.87; 95% CI, 0.76–1.00; P = .055).[377] There were no statistically significant effects on distant metastasis-free survival (DMFS) 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.

Table 6. High-Dose Interferon[a]

Trial[b]	References	IFN type	Patients, n		Median Follow-up	Statistically Significant Impact of IFN	
			IFN	Obs		Relapse-free Survival[c]	Survival[d]
ECOG 1684	Kirkwood 1996[378] Kirkwood 2004[366]	2b	143	137	6.9 y 12.6 y	Yes; *P* = .0023 Yes; *P* = .02	Yes; *P* = .0237 No
ECOG 1690	Kirkwood 2000[365] Kirkwood 2004[366]	2b	215	212	4.3 y 6.6 y	Yes; *P* = .05 Trend; *P* = .09	No No
ECOG 1694	Kirkwood 2001[379] Kirkwood 2004[366]	2b	440	440[e]	1.3 y 2.1 y	Yes; *P* = .0027 Yes; *P* = .006	Yes; *P* = .0147 Yes; *P* = .04
ECOG E2696	Kirkwood 2001[379] Kirkwood 2004[366]	2b	72[f]	35[f]	1.9 y 2.8 y	Yes; *P* = .03 No	No No
Sunbelt Trial	McMasters 2016[380]	2b	112	106	5.9 y	No	No

IFN, interferon; NR, not reported; Obs, observation

[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.

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 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.[340] Eligible patients had fully resected stage III cutaneous melanoma, including all except for the lowest risk substage, stage IIIA-N1a (non-ulcerated primary tumor with micrometastasis in one 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 with 95% CI, 0.58–0.97; *P* = .03). Median OS and 5-year OS rate were not significantly different between the two treatment groups. Although the overall percent of patients who experienced grade 3–5 adverse events (AEs) 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 (See *Checkpoint Immunotherapy Treatment Administration* section below). Ipilimumab, a monoclonal antibody directed to the immune checkpoint receptor CTLA-4, has been shown to significantly improve PFS and OS in patients with unresectable or metastatic melanoma (See Ipilimumab: Efficacy section below), and originally received FDA approval in 2011 for treatment of patients with metastatic melanoma. Based on its efficacy for treating metastatic disease, the phase 3 double-blind, randomized, multicenter, international EORTC 18071 trial compared 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 had their primary tumor excised with adequate margins and complete regional lymphadenectomy, but none had received systemic therapy for melanoma.[341] 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).[341,381] 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 >1 mm diameter who have undergone complete resection, including total lymphadenectomy.[381] 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.[341,381]

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.[341,381] In contrast, for treatment of unresectable or metastatic disease, the recommended ipilimumab dose is much lower (3 mg/kg) and the treatment duration much shorter (every three weeks for a total of four doses).[381] Ipilimumab is associated with a variety of immune-related adverse events (irAEs), and the frequency and severity of these toxicities has been shown to increase with dose.[382-385] A meta-analysis including 1265 patients from 22 clinical trials found that the risk of developing an irAE (any grade) was three-fold higher with ipilimumab 10 mg/kg versus 3 mg/kg.[383]

In EORTC 18071, grade 3–4 AEs were more common with ipilimumab versus placebo (54% vs. 25%), as were irAEs (grade 3: 37% vs. 2%; grade 4: 6% vs. <1%).[341] Fatal ipilimumab-related AEs occurred in 5 patients (1%), and included colitis with gastrointestinal perforation (n = 3), myocarditis (n = 1), and multi-organ 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 above 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 five 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 1) resected stage IIIA with metastases >1 mm; 2) resected stage IIIB-C; or 3) resected 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. 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 of 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 following 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).[218] The authors concluded that radiation 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 SLNB showed that adjuvant RT was associated with improved local control, particularly in patients with positive excision margins or primary melanoma with Breslow thickness >4 mm or located in the head and neck region. [386] 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 DMFS.[387] 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.[388] Results from these four and one smaller retrospective study[389] suggest that adjuvant RT improves local control in patients with desmoplastic melanoma, a hypothesis that is being tested in an ongoing phase III trial comparing adjuvant RT with observation following resection of neurotropic melanoma of the head and neck (NCT00975520).[390]

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.[391] Six hundred fifteen patients were evaluated 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 only 10% of the patients selected to receive adjuvant RT, compared to 41% of the non-radiated patients. 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 of 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.[392,393] One retrospective analysis suggested that the benefit of RT for regional control may be associated with doses of at least 50 Gy.[394] Interpretation of these results should take into consideration selection bias and many 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 nonmetastatic disease and palpable lymphadenopathy at diagnosis or as an isolated palpable site of relapse.[395] Eligible patients were required to have an LDH <1.5 times the upper limit of normal, as well as ≥1 parotid, ≥2 cervical or axillary or ≥3 groin positive nodes, a maximum nodal diameter ≥3 cm in neck, ≥4 cm in the axilla or groin, or nodal extracapsular extension.[396] Patients were treated with lymphadenectomy followed by either adjuvant radiation (48 Gy in 20 fractions) to the nodal basin or observation.[395] 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.[395] 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 AEs.

Various fractionation schemes for postoperative adjuvant radiation have been evaluated in retrospective studies.[386,397-401] Hypofractionated radiotherapy appears to be equally as effective as standard fractionation. These studies have shown moderate toxicity associated with adjuvant RT. While 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.[402-408] 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. However, these trials included very few patients with melanoma—likely less than 60 patients all together—and did not report results specifically from patients with melanoma. The largest of these prospective randomized trials included 18 patients with melanoma, and 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.[408] 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.[409,410] 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.

There are no good prospective randomized trials testing adjuvant SRS following surgery for patients with brain metastases from melanoma, but 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 by 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 following 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 OS 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 above.[396] 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*.

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:

1) Local therapy: Local treatments reduce the morbidity of in-transit lesions but have a low/variable effect on the appearance of new lesions.
2) 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.
3) Systemic therapy: Systemic treatments have antitumor effects on existing in transit lesions and may help delay/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 and tumor burden, defined by the size, location, and number of tumor deposits. Since 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/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.[411]

For patients for whom resection is not feasible, prior resections have been unsuccessful, or who refuse surgery, non-surgical 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 he most promise are summarized in Table 7.

Talimogene Laherparepvec

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.[412-415] These studies and others led to the development of talimogene laherparepvec (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.[416] A recent phase 3 trial in select patients with unresectable stage IIIB-IV melanoma randomized subjects to intralesional injection T-VEC versus subcutaneous injection of GM-CSF.[417] Patients were required to have at least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions >10 mm in diameter, bidimensionally measurable disease, and limited distant metastatic disease (with specific definitions). T-VEC produced clinically significant durable response rates (DRRs) in injected tumors, and a bystander effect on some uninjected non-visceral and visceral tumors (Table 7).[418] At a median follow-up of 44 months (range 32–59 months), patients treated with T-VEC compared with GM-CSF showed a higher DDR (16.3% vs. 2.1%, $P < .001$) and overall response rate (26.4% vs. 5.7%, $P < .001$; complete response in 11% vs. <1%).[417]

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%).

For T-VEC, common toxicities (treatment-emergent in ≥20%, any grade) were fatigue, chills, pyrexia, nausea, flu-like illness, injection-site pain, and vomiting.[417] Treatment-related toxicities of grade 3-4 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 7). 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.[419] Intralesional injection of IL-2 is far less toxic than high-dose IV IL-2. Grade 1-2 adverse effects are common but manageable, and grade 3-4 toxicities are extremely rare.[419-421] 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, and sometimes stomach pain, diarrhea, and headache) that are usually mild and often respond to analgesics.[419,420,422]

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[423]).

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 7).[424-426] Although initial response

rates are high for injected lesions, intralesional BCG is associated with a number of significant local and occasional systemic adverse effects.[425-427] 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).[428,429] It has similar activity to other intralesional agents, but is not currently available outside of the clinical trial setting (NCT02288897).

Table 7. Intralesional Injection

Injection Agent	Key Published Clinical Studies	Response Rates	
		Injected Lesions	Uninjected Lesions
Talimogene laherparepvec (T-VEC)	• Phase III trial[417,418]	≥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[419,420] and retrospective/observational analyses[430-433] • 2014 systematic reviews and meta-analysis[421]	CR: 67%–96% •80% for dermal •73% for subcutaneous	No responses seen in two phase 2 trials
Bacillus Calmette-Guérin (BCG)	• >10 prospective pilot/retrospective studies[a] • 1 prospective randomized study[426]	CR: •90% for dermal •45% for subcutaneous	Occasional responses observed
Rose Bengal	• Phase I trial[428] • Phase II trial[429]	OR: 46%–58%	OR: 27%

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,[425] Morton et al. 1974,[434] and Table 5 in Tan et al. 1993,[424] a pooled analysis of 15 studies.

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 non-comparative retrospective analyses (15–100 patients/study).[435-441] Ablation can be effectively achieved with minimal toxicity,[435,437,438,441] but this technique has largely been supplanted by more contemporary approaches.

Topical Therapy

In patients with in-transit/locally metastatic disease, case reports suggest that imiquimod monotherapy can provide partial and complete responses in patients with cutaneous metastases, but is less likely to be

effective on deep dermal or subcutaneous metastases.[442-446] 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.[444,447-453]

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.[454-461] One retrospective study included 50 patients with in-transit cutaneously metastatic melanoma treated for at least one month with DPCP.[462] 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.

Radiation

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*.

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,[463-468] but also associated with increased toxicity.[469,470] 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.[471,472] 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.[472-475] 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%).[474] 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.[474] 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.[476] 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.[477] 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,[478] amenable to repeated applications,[479] and safe for use in elderly patients.[480] Melphalan is commonly used for ILI, often with actinomycin D.[481] Addition of papaverine for cutaneous vasodilation has been shown to increase response rate but also the risk of regional toxicity.[482,483] 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.[482,484-488] An analysis of seven studies, including 576 patients, primarily with stage III disease, 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%.[481] A smaller pooled analysis of two additional studies (N = 58), one a non-comparative phase II study (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%).[489] 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 a 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 >10 mm in diameter, may be appropriate candidates for intralesional injection with T-VEC. Intralesional injection with T-VEC is a recommended option for 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 is injection with BCG or IFN. All of these options are category 2B recommendations.

Based on non-comparative 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 be considered as 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 increasing be considered as a first-line treatment option for regionally recurrent melanoma. See *Systemic Therapy for Advanced Melanoma* for treatment options.

Given the number of options available, clinical judgment and multidisciplinary consultation is often helpful to determine the order of therapies.

Treatment for Distant Metastatic Disease (Stage IV)

Systemic Therapy for Advanced Melanoma

The therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents, which have demonstrated better efficacy than traditional chemotherapy. The first generation of novel targeted and immunotherapy agents (ie, vemurafenib, dabrafenib, ipilimumab) demonstrated significantly improved response rates and outcomes compared with conventional therapies. Subsequently, a number of ongoing or recently completed phase II and phase III trials testing new immunotherapies, targeted therapies, and combination regimens have yielded noteworthy results.[93,417,490-501] A second generation of effective agents and combination regimens are now available for treatment of advanced unresectable or metastatic melanoma.

Checkpoint Immunotherapy

The immune system may be capable of identifying and destroying certain malignant cells, a process called immunosurveillance. Conditions or events that compromise the immune system can lead to cancer cells escaping immunosurveillance.[502-504] Once cancer cells have escaped immunosurveillance and have begun to proliferate, their genetic and phenotypic plasticity enables them to develop additional mechanisms by which the nascent tumor can evade, thwart, or even exploit the immune system.[502-504] Immunotherapies are aimed at augmenting the immune response to overcome or circumvent the immune evasion mechanisms employed by cancer cells and tumors. Some of the most effective immunotherapies target immune checkpoints exploited by cancers to decrease immune activity. For example, activation of T helper cells upon binding to antigens on the antigen-presenting cell (APC) can be modulated by other receptor-ligand interactions between the two cells. Cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death protein 1 (PD-1) are two examples of receptors on T-cells that upon ligand binding trigger a signalling cascade that inhibits T-cell activation, limiting the immune response.[505-508] Antibodies against these receptors (eg, ipilimumab, nivolumab, pembrolizumab) prevent receptor-ligand interaction, removing the inhibition of T-cell activation and 'releasing the brake' on the immune response.[509-511]

Ipilimumab

Ipilimumab is a monoclonal antibody directed against the immune checkpoint receptor CTLA-4. Two phase III trials in patients with unresectable stage III or stage IV melanoma support the use of ipilimumab for advanced disease (Table 8). Results from these trials showed that ipilimumab improved response rates, response duration, PFS, and OS in patients with previously treated or previously untreated advanced disease.[512,513] Most importantly, extended follow-up showed that ipilimumab resulted in long-term survival in approximately 20% of patients (5-year OS: 18% vs. 9% for dacarbazine),[514] consistent with findings from phase II trials.[515,516,517] Safety results from these trials showed that ipilimumab is associated with a substantial risk of irAEs, including grade 3-4 events (Table 8) and drug-related deaths (7 in CA184-002).[512] Even higher rates of grade 3-4 irAEs were observed in patients treated with ipilimumab in CA184-024 (Table 8), possibly due to the high dose used (10 mg/kg), or due to combination therapy with dacarbazine, or both.[513] Combination therapy with ipilimumab and dacarbazine therefore is not used in clinical practice, and the FDA-recommended dose of ipilimumab is 3 mg/kg rather than 10 mg/kg.[381] Immune-related AEs associated with ipilimumab and other checkpoint

inhibitor regimens are detailed in the *Toxicity of Checkpoint Immunotherapies* section.

Given that treatment options may be limited for heavily pretreated patients who have progressed after checkpoint inhibitor therapy, it is noteworthy that reinduction therapy with ipilimumab was administered to a small number of patients in CA180-002 who had progressed after showing initial clinical benefit (responses or stable disease lasting ≥3 months). Disease control (CR, PR, or SD) was achieved upon ipilimumab reinduction in most of these patients (20/31).[512,518] The frequency and types of ipilimumab-related irAEs seemed similar for reinduction as for initial treatment, and patients who experienced toxicities during the initial round of therapy did not necessarily experience the same irAEs upon reinduction.[518]

Although the pivotal phase III ipilimumab trials excluded patients with active CNS metastases, results from an open-label, phase II study (CA184-042; Table 8) showed a modest CNS disease control rate and acceptable toxicity in patients with brain metastases.[136]

Table 8. Ipilimumab Trials in Advanced Melanoma[a]

Trial		Patients		Treatment Arms	Response[c]			PFS[d]	OS[d]	Grade 3-4 irAEs[e]
Name and References	Phase Design	Tx Naive[b]	CNS Mets		Rate	Onset	Duration			
CA184-002 NCT00094653[512]	III RDB	None	12%[f]	• Ipi + gp100 (n = 403)	6% *P* = .04	3.3	17%[g]	2.8 *P* < .05[h]	10.0 *P* < .001	10%–15%
				• Ipi (n = 137)	11% *P* = .001	3.2	60%[g]	2.9 *P* < .001[h]	10.1 *P* = .003	
				• gp100 (n = 136)	2%	2.7	0[g]	2.8	6.4	3%
CA184-024 NCT00324155[513]	III RDB	100%	None	• DTIC + ipi (n = 250)	15% *P* = .09	NR	19.4 *P* = .03	NR *P* = .0006[g]	11.2 *P* < .001	38%
				• DTIC + pbo (n = 252)	10%	NR	8.1	NR	9.1	4%
CA184-042 NCT00623766[136]	II OL	≥71%	100%	• Ipi, ASX[i] (n = 51)	10%	NR	NR	1.4	7.0	NR
				• Ipi, Sx[i] (n = 21)	5%	NR	NR	1.2	3.7	NR

ASX, patients with asymptomatic brain metastases; CNS Mets, percent of patients with central nervous system metastases at baseline; CR, complete response; DTIC, dacarbazine; gp100, gp100 peptide vaccine; ipi, ipilimumab; irAEs, immune-related adverse events; Sx, patients with symptomatic brain metastases; NR, not reported; OL, open-label; pbo, placebo; R, randomized; RDB, randomized, double-blind; Tx, treatment.

[a]Unresectable stage III or stage IV melanoma.
[b]Percent of patients with previously untreated advanced disease.
[c]Response rate is the percentage of patients who achieved complete or partial response. Time to onset is the median time to response, given in months. Response duration is given as the median, in months, unless otherwise indicated. P values are for comparisons with the control arm.
[d]Median PFS and OS are given in months. Median duration, P value, and HR were determined using the Kaplan-Meier method.
[e]Percent of patients who experienced any type of treatment-related irAE of grade 3 or 4.
[f]Patients with active CNS metastases were excluded from the trial.
[g]Percent of patients with response duration >24 months.
[h]Although median PFS was similar across arms. P values for PFS and OS refer to differences in Kaplan-Meier survival distributions.
[i]Results were reported for patients with asymptomatic versus symptomatic brain metastases.

Anti-PD-1 Agents

While anti CTLA 4 therapy seems to interfere primarily with the feedback mechanism at the interface between T cell and antigen-presenting dendritic cell, anti-PD-1 inhibitors are thought to interfere primarily with the feedback mechanism at the interface of T cell and tumor cell.[519]

Pembrolizumab

Randomized trials in patients with unresectable stage III or stage IV metastatic disease have shown that pembrolizumab (monotherapy), like nivolumab, improves response and PFS compared with chemotherapy or ipilimumab (monotherapy), and is associated with lower risk of AEs (Table 9).[500] Results from KEYNOTE-006 showed that pembrolizumab also improved OS compared with ipilimumab.[500] The efficacy and safety of pembrolizumab did not appear to be significantly affected by the dose level (2 mg/kg vs. 10 mg/kg) and frequency (every 2 weeks [Q2W] or every three weeks [Q3W]), and all the regimens tested in these trials improved response and outcomes compared with controls.[495,500,520]

Table 9. Pembrolizumab Trials in Advanced Melanoma[a]

Trial		Patients				Response[d]					
Name and References	Phase Design	Tx Naive[b]	*BRAF* V600 Mut	Brain Mets[c]	Treatment Arms	Rate	Onset	Duration	PFS[e]	OS[e]	Grade 3-4 AEs[f]
KEYNOTE-001 NCT01295827[520]	I R, OL, E	None[g]	18%	9%	• Pembro 2 mg/kg (n = 89)	26%	2.8	ND	5.1	58%	15%
					• Pembro 10 mg/kg (n = 84)	26%	2.8	ND	3.2	63%	8%
KEYNOTE-002 NCT01704287[495]	II R, OL	None[g]	23%	NR	• Pembro 2 mg/kg (n = 180)	21% *P* < .0001	3	ND	2.9[i] *P* < .0001	ND	11%
					• Pembro 10 mg/kg (n = 181)	25% *P* < .0001	3.5	ND	2.9[i] *P* < .0001	ND	14%
					• Chemo[h] (n=179)	4%	3	37	2.7	ND	26%
KEYNOTE-006 NCT01866319[500]	III R, OL	34%	36%	9%	• Pembro Q2W (n = 279)	34% *P* < .001	2.8	8.3	5.5 *P* < .001	74% *P* < .0005	13%
					• Pembro Q3W (n = 277)	33% *P* < .001	2.8	ND	4.1 *P* < .001	68% *P* = .0036	10%
					• Ipi (n = 278)	12%	2.9	ND	2.8	58%	20%

BRAF V600 Mut, percent of patients with a mutation in *BRAF* at V600; Chemo, chemotherapy; CNS Mets, percent of patients with central nervous system metastases at baseline; E, expansion; ipi, ipilimumab; Mut, mutated; ND, not determined because longer follow-up is needed; NR, not reported; OL, open label; pembro, pembrolizumab; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomized.

[a]Unresectable stage III or stage IV melanoma.

[b]Previously untreated advanced disease.

[c]Patients with active CNS metastases were excluded from the trials.

[d]Response rate is the percentage of patients that achieved complete or partial response. Time to onset is the median time to response, given in months. Response duration is given as the median, in months, unless otherwise indicated. P values are for comparisons with the control arm.

[e]Median PFS is given in months. OS is given as 1-year rate. Median duration, P value and HR were determined using the Kaplan-Meier method.

[f]Percent of patients who experienced any type of treatment-related AE of grade 3 or 4.

[g]All were previously treated with ipilimumab and progressed; patients with *BRAF* mutations were also previously treated with BRAF or MEK inhibitors, or both.

[h]Investigator's choice chemotherapy.

[i]Median PFS and HRs varied by method of assessment; for all analyses *P* < .0001.

Nivolumab

Two phase III clinical trials have demonstrated nivolumab efficacy in previously untreated unresectable stage III or stage IV melanoma (Table 10). Results from Checkmate 066 showed that nivolumab improved response rate, PFS, and OS compared with chemotherapy. The percent grade 3-4 AEs was lower with nivolumab compared to chemotherapy.[496] Remarkably, the survival curve suggests that nivolumab may lead to long-term survival in at least 50% of patients. Results from Checkmate 067 showed that nivolumab (monotherapy) improved response rate and PFS compared with single-agent ipilimumab, and was associated with lower toxicity.[492]

The results of Checkmate 066 and 067 demonstrated that in the first-line setting nivolumab is a better option than chemotherapy or ipilimumab for patients with unresectable or metastatic disease. An ongoing trial, Checkmate 037, has shown that nivolumab also improves response rate compared with chemotherapy in patients with previously treated unresectable stage III or stage IV melanoma (Table 10).[490] Safety results suggest that nivolumab may be better tolerated than chemotherapy in heavily pretreated patients with advanced disease.[490] Further follow-up is needed to verify whether nivolumab improves PFS or OS in patients with previously treated advanced disease.

Table 10. Nivolumab Trials in Advanced Melanoma[a]

Trial		Patients			Treatment Arms	Response[d]			PFS[e]		OS[e]		Grade 3-4 AEs[f]
Name and References	Phase Design	Tx Naive[b]	BRAF V600 Mut	CNS Mets[c]		Rate	Onset	Duration					
CheckMate 066 NCT01721772[496]	III RDB	100%	0%	3.6%	• Nivo (n = 210) • DTIC (n = 208)	40% 14% *P* < .001	2.1 2.1	ND 6	5.1 2.2	*P* < .001	73% 42%	*P* < .001	12% 18%
CheckMate 067 NCT01844505[492]	III RDB	100%	32%	3.6%	• Nivo + ipi (n = 314) • Nivo (n = 316) • Ipi (n = 315)	57% *P* < .001 44% *P* < .001 19%	2.8 2.8 2.8	ND ND ND	11.5 6.9 2.9	*P* < .001 *P* < .001	ND ND ND		55% 16% 27%
CheckMate 069 NCT01927419[499]	II RDB	100%	23%	3%[g]	• Nivo + ipi (n = 95) • Ipi (n = 47)	59% 11% *P* < .001	~3 ~3	ND ND	8.5-ND[i] 2.7-4.4[i]	*P* < .001	ND ND		54% 24%
CheckMate 037 NCT01721746[490]	III R, OL	0%	22%	19%[g] 14%[g]	• Nivo (n = 272) • Chemo[h] (n = 133)	31% 8%	2.1 3.5	ND 3.5	4.7 4.2	NS	ND ND		9% 31%

BRAF V600 Mut, percent of patients with a mutation in *BRAF* at V600; Chemo, chemotherapy; CNS Mets, percent of patients with central nervous system metastases at baseline; CR, complete response; DTIC, dacarbazine; ipi, ipilimumab; nivo, nivolumab; PR, partial response; ND, not determined because longer follow-up is needed; NS, not statistically significant; OL, open-label; RDB, randomized, double blind.

[a]Unresectable stage III or stage IV melanoma.

[b]Previously untreated advanced disease.

[c]Patients with active CNS metastases were excluded from the trials.

[d]Response rate is the percentage of patients that achieved complete or partial response. Time to onset is the median time to response, given in months. Response duration is given as the median, in months, unless otherwise indicated. P values are for comparisons with the control arm.

[e]Median PFS is given in months. OS is given as 1-year rate. Median duration, P value, and HR were determined using the Kaplan-Meier method.

[f]Percent of patients who experienced any type of treatment-related AE of grade 3 or 4.

[g]Patients with a history of brain metastases.

[h]Investigator's choice chemotherapy: single-agent dacarbazine or carboplatin/paclitaxel combination.

[i]Reported separately for patients with *BRAF* V600 mutation and *BRAF* wild-type disease.

Anti-CTLA-4/Anti-PD-1 Combination Therapy

As shown in Table 10, results from two randomized trials demonstrated that ipilimumab/nivolumab combination therapy significantly improved response and PFS compared with ipilimumab monotherapy in patients with previously untreated unresectable stage III or stage IV disease.[492,499] Further follow-up is needed to determine whether nivolumab/ipilimumab combination therapy improves OS compared with single-agent ipilimumab. Both these trials also showed substantially increased toxicity with immune checkpoint combination therapy versus monotherapy.

Anti-PD-1 Therapy in Patient Subpopulations

BRAF Mutation Status

Subgroup analyses in the Checkmate and KEYNOTE trials showed that both patients with *BRAF* mutant tumors and those with *BRAF* wild-type tumors derived clinical benefit from anti-PD-1 therapy compared with controls (single-agent ipilimumab or chemotherapy).[490,492,495,500] Likewise, subgroup analyses in CheckMate 067 and 069 showed improved efficacy with nivolumab/ipilimumab combination therapy compared with ipilimumab monotherapy regardless of *BRAF* mutation status.[492,499]

PD-L1 Expression

To determine whether the PD-1 ligand (PD-L1) could be used to identify candidates for anti-PD-1 therapy, PD-L1 expression was assessed in tumor samples from patients in the CheckMate and KEYNOTE trials, and expression level cutoffs were chosen to divide patients into "PD-L1 positive" and "PD-L1 negative" subgroups.[490,492,496,499,521] Across trials results showed that for *both* subgroups, anti-PD-1 monotherapy provided clinical benefit compared with controls (single-agent ipilimumab or chemotherapy), and nivolumab/ipilimumab combination therapy improved efficacy compared with ipilimumab. The apparent prognostic value of PD-L1 may have been limited by the expression assays and cutoffs used in these studies. Although PD-L1 expression continue to be developed, in current form they are not sufficiently reproducible, widely available, nor discriminative for screening patients with melanoma.

Brain Metastases

In the CheckMate and KEYNOTE trials, 3% to 19% of patients had brain metastases (Tables 9 and 10). Ongoing trials have been designed to specifically address the safety and efficacy of anti-PD-1 in patients with melanoma brain metastases.[522-524]

Before or After Anti-CTLA-4 Therapy

Ongoing studies are aimed at determining the efficacy of sequential monotherapy with ipilimumab and PD-1 inhibitor. Preliminary results from a randomized phase II trial show similar safety but improved response for patients treated with nivolumab followed by ipilimumab compared with patients who received these therapies in the reverse order.[525]

Checkpoint Immunotherapy Treatment Administration

The ipilimumab treatment regimen of 3 mg/kg every three weeks for four doses is well supported by clinical trial data and approved by the FDA.[381,512,513] For anti-PD-1 agents, however, there are fewer data to support the optimal dose and duration of treatment. Tables 11 through 13 summarize the treatment dosing and duration used in the pivotal trials supporting anti-PD-1 agents for use in unresectable or metastatic melanoma. The FDA-recommended dosing regimen for single-agent nivolumab matches that used in all 3 phase III trials shown in Table 11: 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity.[490,492,496,526] The FDA-recommended dosing for pembrolizumab is 2 mg/kg every 3 weeks until disease progression or unacceptable toxicity.[527] The FDA-recommended dosing regimen for nivolumab/ipilimumab combination therapy is nivolumab 1 mg/kg followed by same-day ipilimumab 3 mg/kg, every 3 weeks for 4 doses; then single-agent nivolumab 3 mg/kg every 2 weeks until disease progression or toxicity.[381,526]

Although the product labels for nivolumab and pembrolizumab indicate that treatment should continue until disease progression or unacceptable toxicity,[526,527] the published trials allowed shorter or longer treatment in certain situations. Discontinuation is common among patients treated with anti-PD-1 therapy, and hence clinical experience with treatment beyond one year is currently limited. For the trials listed

in the tables, results published thus far (median follow-up <2 years) show discontinuation rates of 45% to 77% in patients treated with anti-PD-1 therapy. In the KEYNOTE-002 study, pembrolizumab was administered for a maximum of 24 months. Further follow-up should indicate whether anti-PD-1 treatment beyond two years is needed to maintain disease control. Studies are needed to explore this question and test whether switching to lower-frequency maintenance therapy is sufficient to maintain long-term clinical benefit.

Table 11. Nivolumab Treatment Regimens

Trial	Dosing	Treatment Duration
CheckMate 066[496]	3 mg/kg Q2W	• Until disease progression or unacceptable toxicity. • Patients who had clinical benefit could opt for treatment beyond progression, provided they had not experienced substantial AEs.
CheckMate 067[492]		
CheckMate 037[490]		

Table 12. Pembrolizumab Treatment Regimens

Trial	Dosing	Treatment Duration
KEYNOTE-002[495]	2 mg/kg or 10 mg/kg Q3W	• Until disease progression or unacceptable toxicity. • Patients with PD at 12-week scan could opt to continue until confirmation of PD at next scan.
KEYNOTE-006[500]	10 mg/kg Q2W or Q3W	• Until disease progression, unacceptable toxicity, or 24 months. • Patients with CR lasting ≥6 months could discontinue after an additional 2 treatments.

Table 13. Ipilimumab/Nivolumab Combination Treatment Regimens

Trial	Dosing	Treatment Duration
CheckMate 067[492]	1 mg/kg nivo + 3 mg/kg ipi (same day), Q3W for 4 doses; then 3 mg/kg nivo monotherapy Q2W	• Until disease progression or unacceptable toxicity. • Patients who had clinical benefit could opt for treatment beyond progression, provided they had not experienced substantial AEs.
CheckMate 069[499]		

Ipi, ipilimumab; nivo, nivolumab; Q2W, once every 2 weeks; Q3W, once every 3 weeks

Toxicity of Checkpoint Immunotherapies

Immunotherapy-associated AEs tend to be inflammatory or autoimmune in nature, often due to reduction in self-tolerance, proliferation of activated T-cells, and pro-inflammatory reactions (release of cytokines) in normal (non-cancerous) organs and tissues.[528-534] The immune system is active throughout the body, and irAEs can occur in any organ.[528,535] Unlike chemotherapy, which directly kills or damages cells, immunotherapy acts indirectly by altering complex multi-step immune processes. Therefore, it is not surprising that for immunotherapy the incidence and severity of toxicities may not correlate well with dose;

rather than reducing dose, withholding or discontinuing treatment is often the recommended method for AE management.

Most of the treatment-related AEs associated with ipilimumab, nivolumab, and pembrolizumab are autoimmune in nature (Table 14). For ipilimumab alone or in combination with anti-PD-1, the most common AEs are cutaneous toxicities (rash, pruritus, and vitiligo), gastrointestinal toxicities (diarrhea/colitis), and fatigue. Aside from these 3 types of toxicities, the most common high-grade toxicities observed in clinical trials are endocrinopathies (eg, hypophysitis, hypo- or hyperthyroidism), and hepatitis (eg, elevated ALT/AST).[381] However, retrospective analyses suggest that clinical trial results may have underestimated the frequency of endocrinopathies.[533,536,537] Other less common toxicities of concern are also shown in Table 14. Many of these toxicities are more frequent with combination ipilimumab plus anti-PD-1 regimens. Gastrointestinal and cutaneous AEs tend to manifest earlier in treatment, whereas the onset tends to be later for endocrinopathies and other rarer toxicities of concern (eg, hepatic, renal, and respiratory; Table 15).

AE rates with anti-PD-1 monotherapy are lower than for ipilimumab single-agent or in combination with anti-PD-1 inhibitor (Table 14). Fatigue and arthralgia are the most frequent AEs in patients treated with anti-PD-1 monotherapy.[492,495,496,500] Pneumonitis and nephritis, although occurring in less than 5% of patients treated with anti-PD-1 monotherapy, may be more common with anti-PD-1 versus ipilimumab monotherapy. Safety guidelines in the FDA labels for nivolumab and pembrolizumab both include specific warnings regarding pneumonitis and nephritis.[381,526,527,538]

Safety data from randomized clinical trials have shown that single-agent nivolumab or pembrolizumab are associated with less toxicity compared with ipilimumab monotherapy (Table 14). Although the proportion of patients who experienced treatment-related AEs of any grade was similar with anti-PD-1 agents (monotherapy) versus ipilimumab, treatment-related AEs associated with anti-PD-1 monotherapy were less likely to be grade 3-4 (Table 14), and less likely to lead to treatment discontinuation.[492,500]

Although there are no data from prospective randomized trials directly comparing nivolumab versus pembrolizumab, these agents appear to have similar safety profiles (Table 14). Both anti-PD-1 monotherapies were associated with notably less diarrhea and pruritus but more hypothyroidism compared with ipilimumab.[492,500]

Safety results from randomized phase II-III trials showed that combination therapy with nivolumab and ipilimumab was associated with higher rates of toxicity compared with single-agent ipilimumab or nivolumab (Table 14).[492,499] Ipilimumab/nivolumab combination therapy increased the total number of patients with treatment-related AEs of any grade, and notably increased the occurrence of grade 3-4 AEs (Table 14) and AEs leading to treatment discontinuation (36% vs. 8%, 15%). For all the toxicities commonly observed with immune checkpoint inhibitors, grade 3-4 AEs occurred more frequently with combination therapy compared with either monotherapy (Table 14).

Table 14. Checkpoint Immunotherapies: Treatment-Related Toxicities[a,b]

Study:	CheckMate 067 and 069[492,499]						KEYNOTE-006[500]			
Agent:	Ipilimumab		Nivolumab[b]		Ipilimumab + Nivolumab		Ipilimumab		Pembrolizumab	
Grade:	3–4	Any	3–4	Any	3–4	Any	3–5	Any	3–5	Any
All types	24–27%	86–93%	16%	82%	54–55%	91–96%	20%	73%	10–13%	73–80%
Diarrhea	6–11%	****	2%	**	9–11%	*****	3%	**	1–3%	**
Colitis	7–9%	*	1%		8–17%	**	6%	*	1–2%	
Rash	≤2%	***	1%	***	5%	****	1%	*	0	*
Pruritus	<1%	****	0	**	1–2%	****	<1%	***	0	*
Vitiligo	0	*	<1%	*	0	*	0		0	*
Fatigue	≤1%	****	1%	***	4–5%	****	1%	**	<1%	**
Nausea	1–2%	**	0	*	1–2%	***	<1%	*	<1%	*
Vomiting	<1%	*	<1%	*	1–3%	**	0	*	<1%	
Decreased appetite	<1%	*	0	*	<1%	**	0	*	0	*
Pyrexia	<1%	**	0	*	1–3%	**	0		0	
Arthralgia	0	*	0	*	<1%	*	1%	*	<1%	*
Myalgia	0[b]	*	NR	NR	0[b]	*	<1%		<1%	*
Asthenia	0[b]	*	NR	NR	0[b]	*	1%	*	<1%	*
Headache	<1%	*	0	*	≤2%	*	0		0	
Dyspnea	0	*	<1%		1–3%	*	<1%		<1%	
Elevated ALT/AST	≤2%		1%		6–11%	**	1%		<1%	*
Hypophysitis	2–4%	*	<1%		2%	*	1%		<1%	
Elevated lipase (pancreatitis)	2%[b]		NR	NR	9%[b]	*	NR	NR	NR	NR
Hypothyroidism	0	**	0	*	<1%	**	0		<1%	*
Hyperthyroidism	0		0		≤1%	*	<1%		0	*
Pneumonitis	≤2%		<1%		1–2%	*	<1%[c]		<1%[c]	
Nephritis	0[b,d]		NR	NR	1%		0[d]		0[d]	

The percent of patients affected by specific AEs (any grade) was rounded to the nearest 10%, then assigned one asterisk (*) for every 10% of patients effected.
NR, not reported.
[a]Aside from nephritis, specific AEs listed occurred in ≥10% of patients for at least one checkpoint immunotherapy regimen.
[b]Data available from only one of two trials.
[c]Any cause (not only treatment related).
[d]Nephritis includes elevated blood creatinine and renal failure.

Table 15: Kinetics and Characteristics of Immune-Related Adverse Events Associated with Ipilimumab[a]

	Time to Onset[b,d]	Time to Resolution[b,d]	IrAE Resolution Rate[c,d]	IrAE Management Techniques Employed[d]
Gastrointestinal (diarrhea, colitis) 383,385,539-547	Median: 3 to 8 weeks 540,542 Range: <3 to 20 weeks 539,540,542,547-549	Median: 3 to 8 weeks 385,492,499,541,542 Range: <1 to 34 weeks 542,547	88-100% 385,492,499,540,542,544,545	• Ipilimumab stopped • Corticosteroids (IV, oral) • Infliximab for refractory cases • Budesonide • Antidiarrheals, antiemetics, antacids • Hydration (IV) • Colectomy for extremely serious or persistent cases
Cutaneous (rash, pruritus, vitiligo) 383,541,543-545	Range: ≤4 to 10 weeks 383,545	Median: 3.3 to 12.4 weeks 492,499,541	74-85% 492,499,544,545	• Ipilimumab stopped • Corticosteroids (topical, oral) • Antihistamines
Endocrine (hypophysitis, hypothyroidism, hyperthyroidism) 383,533,536,537,542,543,545,550-552	Median: 8.4 to 11 weeks 536,537 Range: 5 to 36 weeks 536,542,545,550-552	Median: 10.5 to 15 weeks[536] Range: 1 to 92 weeks 385,536,542,545	25-29%[e,383,492] By axes[f]: 0/28 (0%) for adrenal insufficiency to 19/24 (79%) for enlarged pituitary[536,551,552]	• Ipilimumab stopped • Corticosteroids (IV) • Hormone replacement therapy
Hepatic (elevated ALT/AST) 385,541-543,545,550,553-555	Range: <3 to 11.6 weeks 542,545,550,553,555	Range: 4 to 26 weeks 385,492,541,545,553,555	23/24 (96%) 385,492,545,550,553,555	• Ipilimumab stopped • Corticosteroids • Immunosuppressive therapies (tacrolimus, mycophenolate, antithymocyte globulin) for refractory cases • Cotrimoxazole and valganciclovir prophylaxis against opportunistic infection during immunosuppressant treatment
Renal (elevated creatinine, renal failure)[556,557]	Range (n=6): 6 to 12 weeks[556]	Median (n=3): 4.6 weeks 492	8/8 (100%) 492,556	• Ipilimumab stopped • Corticosteroids
Respiratory (pneumonitis, dyspnea, cough)[542,549]	Range (n=8): 4.7 to 35.6 weeks[542]	Range: 1.4 to 24 weeks 492,499,542,549	11/14 (79%) 492,499,542,549	• Corticosteroids (IV, oral) • Cotrimoxazole IV • IgG for humoral immune defect

[a]Combined results from small sets of patients from clinical trials, retrospective analyses, or case studies
[b]For time to onset and time to resolution, median(s) provided are from studies with at least 10 patients with the irAE of interest, and ranges include data from studies with fewer patients. The number of patients with the irAE of interest (n) is provided for data based on fewer than 10 patients.
[c]Resolution rate was defined as the percent of patients with "significant improvement" or improvement to grade 1 or lower out of the total number of patients in which the irAE was actively managed and sufficient follow-up was available. For common irAEs, management and resolution data were available for larger sample sizes (ie, 2 or more studies with ≥10 patients with the irAE of interest), so the range of resolution rates is reported. For rarer irAEs for which the data on management and resolution are more limited, data from multiple smaller studies were combined to report the total number of patients in which the irAE resolved (n) out of the total number of patients in in which the irAE was actively managed and sufficient follow-up was available (N).
[d]Management techniques listed were used in studies that reported on irAE resolution, and may include methods that are no longer recommended. Data on irAE resolution is based on patients whose irAEs that were managed using some or all of the methods listed.
[e]Resolution rates from studies reporting the percent of patients for whom all their endocrinopathies resolved.
[f]Resolution rates from studies reporting separately on different signs, including pituitary enlargement and specific hormonal insufficiencies.

Management of Immune-related Toxicities

Much of the management of irAEs associated with checkpoint immunotherapies has evolved in centers using these agents in the context of clinical trials. Aside from one randomized controlled trial testing prophylactic budesonide (described below), management recommendations are based on published expert opinion or results from small sets of patients from clinical trials, retrospective analyses, or case studies. Table 15 shows combined results from publications reporting irAE management techniques used and the observed resolution rate and timing. These studies found that with the exception of endocrinopathies, most irAEs resolved when managed by withholding ipilimumab and administering corticosteroids.[383,540,542-545,553,556] Although oral corticosteroids have been shown to reverse ipilimumab-associated diarrhea and colitis, results of a phase II placebo-controlled randomized trial showed that prophylactic oral budesonide does not reduce the incidence of moderate to severe diarrhea (grade ≥2) or any other irAE in patients receiving ipilimumab (10 mg/kg every 3 weeks) for unresectable stage III or stage IV metastatic melanoma.[558,559]

Reports indicate that many high-grade or refractory irAEs have been successfully managed using high-dose oral or IV corticosteroids, and that immunosuppressants have been used successfully in some particularly challenging cases of gastrointestinal and hepatic irAEs.[540,545-547,549,560,561] Based on a growing number of case reports, the immunosuppressant infliximab can provide rapid improvement in patients with serious or steroid-refractory colitis.[383,539-543,546-549,561-563] For many cases reported only one dose of infliximab was needed to dramatically improve symptoms.[547 Merrill, 2014 #1858,548,549,561-563] Several immunosuppressants have been used in attempts to manage high-grade liver toxicities: tacrolimus, mycophenolate, 6-mercaptopurine, and antithymocyte globulin.[541,542,553-555] Case reports have shown that administering mycophenolate plus steroids can reverse ipilimumab-associated severe (grade ≥3) hepatotoxicity.[541,542,553]

Endocrinopathies associated with ipilimumab have proved more difficult to manage, and require hormone replacement therapy in addition to corticosteroids (Table 15). Compared with other irAEs associated with ipilimumab, endocrinopathies were less likely to fully reverse and took longer to resolve.[533,536,537,551] Patients with endocrinopathies frequently required ongoing hormone replacement,[383,533,536,550,551] emphasizing the importance of early detection to minimize long-term sequelae. Endocrinopathies often presented as headache, fatigue or asthenia, but sometimes presented with a variety of other symptoms.[383,533,537,543,545,551,564] Affected areas are often the hypothalamic-pituitary-

adrenal axis, thyrotropin axis, and gonadal axis, and were frequently associated with enlargements of the pituitary gland detected by MRI[383,533,536,537,542,551,552].

BRAF-targeted Therapies

Approximately half of patients with metastatic cutaneous melanoma harbor an activating mutation of *BRAF*, an intracellular signaling kinase in the MAPK pathway.[89-91] Most *BRAF*-activating mutations occurring in melanomas are at residue V600, usually V600E but occasionally V600K or other substitutions.[90,565] BRAF inhibitors have been shown to have clinical activity in melanomas with *BRAF* V600 mutations. Inhibitors of MEK, a signalling molecule downstream of BRAF, may potentiate these effects. Recent efficacy and safety data from large randomized trials testing BRAF and MEK inhibitors have significantly impacted the recommended treatment options for patients with *BRAF*-mutation positive advanced melanoma.

BRAF Inhibitor Monotherapy

Vemurafenib and dabrafenib were developed to inhibit BRAF with mutations at V600.[566-568] For patients with previously untreated stage IV or unresectable stage III melanoma, phase III trials (BRIM-3, BREAK-3) have shown that monotherapy with either of these agents improves response rates, PFS, and OS compared with chemotherapy (dacarbazine; Tables 16–18). For both vemurafenib (Table 16) and dabrafenib (Table 17), efficacy in patients with previously-treated advanced disease, including patients who received prior ipilimumab, is supported by single-arm open-label trials (NCT00949702, BREAK-2) showing response rates, median PFS, and median OS similar to those from the phase III trials (BRIM-3, BREAK-3). Phase III trial results show that time to response for BRAF inhibitors (median ~1.5 months) was shorter than with chemotherapy (Table 17), and when compared to data from other trials, appears to be shorter than for checkpoint immunotherapy (median 2.1–3.5 months; Tables 8–10 and 16–18). Responses to BRAF inhibitor monotherapy were relatively short lived, however, with median duration ~5 to 7 months (Tables 16–17). Likewise, PFS and OS Kaplan-Meier curves for vemurafenib and dabrafenib show little or no decline during the first few months of treatment (~1.5 months for PFS, ~3 months for OS), and then abruptly begin to decline.[93,94] Both dabrafenib and vemurafenib have been tested in non-comparative trials (NCT01307397, BREAK-MB) as single-agent therapy in patients with asymptomatic brain metastases (Table 16–17). Response rates for vemurafenib (24%)[494] and dabrafenib (31%–38%, Table 17) were lower than for patients without brain metastases, but are nonetheless notable in the context of this difficult to treat population.

Table 16. Vemurafenib Monotherapy in Advanced Melanoma[a]: Key Trials

Trial		Patients			Treatment Arms	Response[c]			PFS[d]	OS[d]	AEs by Grade[e]		
Name and References	Phase Design	Tx Naive[b]	*BRAF* V600E (K)	Brain Mets		Rate	Onset	Duration			3	4	5
BRIM-3 NCT01006980[92,93]	III R, OL	100%	91% (9%)[f]	NR[g]	• Vem (n = 337) • DTIC (n = 338)	48% *P* < .001 5%	1.5 2.7	NR NR	6.9 *P* < .0001 1.6	13.6 *P* = .0008 9.7	65% 33%	6% 9%	2% 2%
NCT01307397[494]	IV OL	50%	All[h]	23%[g]	• Vem (N = 3222)	34%[i]	NR	7.3	5.6	12.0	45%	3%	3%
NCT00949702[a569]	II OL	None	92% (8%)[f]	<1%	• Vem (N = 132)	53% (40%)	NR	6.7	6.8	15.9	60%	4%	<1%

BRAF V600 Mut, percent of patients with a mutation in *BRAF* at V600; Brain Mets, percent of patients with brain metastases at baseline; DTIC, dacarbazine; Mets, metastases; NR, not reported; R, randomized; OL, open label; vem, vemurafenib.

[a]Unresectable stage III or stage IV melanoma; NCT00949702 included only stage IV melanoma.

[b]Previously untreated advanced disease.

[c]Response rate is the percentage of patients that achieved complete or partial response. Time to onset is the median time to response, given in months. Response duration is given as the median, in months, unless otherwise indicated. P values are for comparisons with the control arm.

[d]Median PFS is given in months. OS is given as 1-year rate. Median duration, P value, and HR were determined using the Kaplan-Meier method.

[e]Percent of patients with AE of any cause (treatment or otherwise). None of these trials reported rates for treatment-related AEs.

[f]Two patients (<1%) had *BRAF* V600D.

[g]Patients with active CNS metastases were excluded from the trials.

[h]All treated patients had a *BRAF* V600 mutation.

[i]Response rate was 24% for patients with brain metastases

[f]Data in parentheses indicate the percent of patients with *BRAF* V600K mutation.

Table 17. Dabrafenib Monotherapy in Advanced Melanoma[a]: Key Trials

Trial		Patients			Treatment Arms	Response[c]			PFS[d]	OS[d]	Grade 3-4 AEs[e]
Name and References	Phase Design	Tx Naive[b]	*BRAF* V600E (K)	Brain Mets		Rate	Onset	Duration			
BREAK-2 NCT01153763[570]	II OL	16%	83% (17%)[f]	0%	Dab (n = 92)	59% (13%)	1.3	5.2 (5.3)	6.3 (4.5)	13.1 (12.9)	27%
BREAK-3 NCT01227889[94,95]	III R, OL	100%	100%	0%	Dab (n = 187) DTIC (n = 163)	50% 5%	1.5 NR	5.5 ND	5.1 2.7 *P* < .0001	18.2 15.6 HR = 0.76	53%[g] 44%[g]
BREAK-MB NCT01266967[571]	II OL	52%	81% (19%)[f]	100%[h]	Dab (n = 172)	31-38% (0-28%)	NR	4.6-6.5[i] (2.9-3.8[i])	3.7-3.8 (1.9-3.7)	7.2-7.6 (3.8-5.0)	22%

BRAF V600 Mut, percent of patients with a mutation in *BRAF* at V600; Brain Mets, percent of patients with brain metastases at baseline; dab, dabrafenib; DTIC, dacarbazine; ND, not determined because longer follow-up is needed; NR, not reported; OL, open label; R, randomized.

[a]Stage IV melanoma; BREAK-3 also included unresectable stage III.
[b]Previously untreated advanced disease.
[c]Response rate is the percentage of patients that achieved complete or partial response. Time to onset is the median time to response, given in months. Response duration is given as the median, in months, unless otherwise indicated. P values are for comparisons with the control arm.
[d]Median PFS is given in months. OS is given as 1-year rate. Median duration, P-value and HR were determined using the Kaplan-Meier method.
[e]Percent of patients who experienced any type of treatment-related AE of grade 3 or 4.
[f]Data in parentheses the percent of patients with *BRAF* V600K mutation.
[g]Percent of patients with AEs of grade 2 or greater. Rates of adverse events of grade ≥3 were not reported.
[h]Patients with active CNS metastases were excluded from the trial.
[i]Intracranial duration of response.

BRAF/MEK Inhibitor Combination Therapy

Despite high initial response rates, half of the patients treated with BRAF-targeted monotherapies relapse within around 6 months, due to development of drug resistance.[94,569,572] Alternate methods for targeting the MAP kinase pathway are being explored as options for overcoming resistance to BRAF inhibitor therapy. Trametinib and cobimetinib are oral small-molecule inhibitors of MEK1 and MEK2, signaling molecules downstream of BRAF in the MAP kinase pathway. Results from a phase III randomized trial (NCT01245062) showed that in patients with *BRAF*-mutated metastatic melanoma not previously treated with BRAF inhibitors, trametinib improves PFS and OS compared with chemotherapy.[572] Although trametinib response rate (22%) was significantly better than chemotherapy (8%, *P* = .01), it was lower than response rates for vemurafenib (48%, 53%) and dabrafenib (50%) from phase II-III trials.[569 92,94] Moreover, in an open-label, phase II study, trametinib failed to induce objective responses in 40 patients previously treated with a BRAF inhibitor.[573]

Although MEK inhibitor monotherapy has limited utility for treating advanced metastatic melanoma, phase III trials have now demonstrated that combination therapy with a BRAF and MEK inhibitor has better efficacy than BRAF inhibitor monotherapy for previously untreated unresectable or metastatic disease (Table 18).[491,497,501] When compared with either single-agent dabrafenib or single-agent vemurafenib, combination therapy with dabrafenib and trametinib improved response rate, duration of response, PFS, and OS.[491,497] Likewise, combination

therapy with vemurafenib and cobimetinib improved response and PFS compared with single-agent vemurafenib.[501] Further follow-up is needed to determine whether vemurafenib/cobimetinib also improves OS.

Few clinical data are available regarding the efficacy of BRAF/MEK inhibitor combination therapy in patients with previously treated advanced melanoma. Results from phase I/II studies (Table 18) showed that in patients who had progressed on previous BRAF inhibitor treatment, dabrafenib/trametinib combination therapy were associated with a relatively poor response rate and duration, PFS, and OS, (although similar time to response) compared with patients who had not received prior BRAF inhibitor treatment.[498,574] A subset analysis in one of these studies (NCT01072175) showed that patients who had rapidly progressed on first-line BRAF inhibitor therapy (time to progression <6 months) derived little or no clinical benefit from second-line BRAF/MEK inhibitor combination therapy compared with patients whose resistance to first-line BRAF inhibitor monotherapy occurred at ≥6 months (response rate: 0% vs. 25%; median PFS: 1.8 months vs. 3.9 months, P = .018).[498]

Table 18. BRAF/MEK Inhibitor Combination in Advanced Melanoma[a]: Key Trials

Trial		Patients			Treatment Arms	Response[c]			PFS[d]		OS[d]		AEs Grade ≥3[e]
Name and References	Phase Design	Tx Naive[b]	*BRAF* V600E (K)	Brain Mets		Rate	Onset	Duration					
BRIM-7[574,575] NCT01271803	Ib OL	49%	93% (7%)	NR[f]	Vem + cobi, dose escalation: • BRAFi naïve (n = 63) • Prior vem[g] (n = 33)	 87% 15%	 1.4 1.5	 12.5 6.7	 13.8 2.8		 28.5 8.4		NR[h]
NCT01072175[498]	I/II OL	None[i]	86% (14%)	14%	• Dab + tram (n = 71)	14%	NR	7.8	3.6		10-11.8		51%
COMBI-d[491] NCT01584648	III RDB	100%	85% (15%)	NR[f]	• Dab + tram (n = 211) • Dab + pbo (n = 212)	69% 53%	*P* = .0014	NR NR	12.9 10.6	11.0 8.8	*P* = .0004	25.1 18.7	*P* = .0107	32%[j] 32%[j]
COMBI-v[497] NCT01597908	III R, OL	100%	90% (10%)	NR[f]	• Dab + tram (n = 352) • Vem (n = 352)	64% 51%	P < .001	NR NR	13.8 7.5	11.4 7.3	*P* < .001	ND 17.2	*P* = .005	52% 63%
Co-BRIM[501] NCT01689519	III RDB	100%	70% (11%)[k]	1%[f]	• Vem + cobi (n = 247) • Vem + pbo (n = 248)	68% 45%	*P* < .001	~1.8 ~1.8	ND 7.3	9.9 6.2	*P* < .001	81%[l] 73%[l]	*P* = .046	65% 59%

BRAF V600 Mut, percent of patients with a mutation in *BRAF* at V600; Brain Mets, percent of patients with brain metastases at baseline; BRAFi naïve, patients without prior BRAF inhibitor treatment; Dab, dabrafenib; cobi, cobimetinib; Mets, metastases; NR, not reported; OL, open label; pbo, placebo; R, randomized; RDB, randomized double blind; tram, trametinib; vem, vemurafenib.

[a]Unresectable stage III or stage IV melanoma.
[b]Patients with previously untreated advanced disease.
[c]Response rate is the percentage of patients that achieved complete or partial response. Time to onset is the median time to response, given in months. Response duration is given as the median, in months, unless otherwise indicated. P values are for comparisons with the control arm.
[d]Median PFS and median OS are given in months. Median durations, P value, and HR are per Kaplan-Meier analysis. P values and HRs are for comparisons with the control arm.
[e]Percent of patients with AE of any cause (treatment or otherwise).
[f]Patients with active brain metastases were excluded from the trial.
[g]Patients who had recently progressed on vemurafenib.
[h]AE rates depended on dose.
[i]All patients progressed on prior BRAF inhibitor.
[j]Treatment-related AEs.
[k]All patients had *BRAF* V600 mutation, but for 20% the exact mutation was unknown.
[l]Median OS was not reached for either arm; rates show the 9-month survival rate.

BRAF and MEK Inhibitor Safety

In phase III trials common toxicities associated with BRAF inhibitor monotherapy (vemurafenib or dabrafenib) were fatigue, arthralgia or myalgia, pyrexia and chills, cutaneous events, alopecia, and cutaneous AEs (Table 19).[93,94,491,497,501] Skin complications occurred with notable prevalence, severity, and variety, including not only rash, pruritus, and

photosensitivity, but also keratoacanthomas, cutaneous squamous cell carcinomas (cSCC), papillomas, hyperkeratoses, and actinic keratoses (Table 19). Safety analyses of phase III trials showed that the risk of toxicity (all grade, grade 3–4) was similar for BRAF/MEK inhibitor combination therapy compared with single-agent BRAF inhibitor therapy (Table 19). For each phase III trial comparing BRAF/MEK inhibitor combination therapy with single-agent BRAF inhibitor therapy, Table 19 shows rates for the most common AEs. As expected, BRAF/MEK inhibitor combination therapy increased the occurrence of some of the most common toxicities, but the specific toxicities affected depends on the particular BRAF/MEK inhibitor combination and BRAF inhibitor monotherapy being compared. Of note, consistent across all phase III trials and other studies, BRAF/MEK inhibitor combination therapy was associated with *lower* rates of alopecia and hyperproliferative cutaneous AEs compared with BRAF inhibitor monotherapy (Table 19).[576] Cross-trial comparisons suggest that diarrhea, elevated ALT/AST, elevated creatinine kinase, rash, and photosensitivity were more prevalent with vemurafenib/cobimetinib combination therapy, whereas pyrexia was more prevalent with dabrafenib/trametinib combination therapy (Table 19).

Table 19: BRAF and MEK Inhibitors: Toxicities[a]

Studies:	COMBI-d[a,491]					Combi-v[497]					Co-BRIM[501]				
Agent:	Dabrafenib			Dabrafenib/ Trametinib		Vemurafenib			Dabrafenib/ Trametinib		Vemurafenib			Vemurafenib/ Cobimetinib	
Grade:	3[b]	Any		3[c]	Any	3[d]	Any		3[e]	Any	3-4[g]	Any		3-4[h]	Any
All types	30%	90%		32%	87%	57%	99%		48%	98%	58%	87%		63%	96%
Systemic AEs:															
Fatigue	<1%	***	~	2%	***	2%	***	~	1%	***	3%	***	~	4%	***
Asthenia						1%	**	~	1%[f]	**					
Arthralgia/Myalgia	0	**	~	<1%	**	4%	*****	>	1%	**	5%	****	>	2%	***
Hypertension						9%[f]	**	<	14%	***					
Headache	0	**	~	0	**	<1%	**	<	<1%[f]	***					
Pyrexia	2%	***	<<	7%	*****	1%	**	<<	4%	*****	0	**	~	2%	***
Chills	<1%	*	<	0	***	0	*	<<	1%	***					
Gastrointestinal AEs:															
Vomiting	<1%	*	~	<1%	*	1%	**	<	1%	***	1%	*	<	1%	**
Nausea	<1%	**	~	0	**	1%	****	~	<1%	****	1%	**	<	1%	****
Diarrhea	1%	*	~	<1%	**	<1%	****	>	1%	***	0	***	<<	6%	******
Constipation						0[f]	*		0	*					
Cough						0	*	<	0	**					
Elevated ALT/AST	<1%		<	2-3%	*	3-4%[f]	**	>	1-3%[f]	*	6%	**	<	8-11%	**
Elevated creatinine kinase						<1%	*	>	0%		0		<<	10%	***
Peripheral edema	0		<	1%	*	<1%	*	~	<1%	*					
Alopecia	0	***	>>	0	*	<1%	****	>>	0	*	0	***	>	0	*
Cutaneous AEs:															
Rash	<1%	**	~	0	**	9%	****	>>	1%	**	5%	****	~	6%	****
Pruritus	0	*	~	0	*	<1%	**	>	0	*					
Dry skin	0	*	~	0	*	<1%	**	>	0	*					
Photosensitivity reaction						<1%	**	>>	0		0	**	<	2%	***
Hyperkeratosis	<1%	***	>>	0	*	1%	***	>>	0		2%	***	>	0	*
Hand-foot syndrome	<1%	***	>>	<1%	*	<1%	***	>>	0						
Skin papilloma	0	**	>	0		1%	**	>>	0						
cSCC and keratoacanthomas	9%	*	>	3%		17%[f]	**	>>	1%		5-8%	*	>	1%	

The percent of patients affected by specific AEs (any grade) was rounded to the nearest 10%, then assigned one asterisk (*) for every 10% of patients effected. Symbols show the whether the percent of patients experiencing the AE was similar in both arms (~), greater in one arm (> or <), or much greater in one arm (>> or <<).

[a]AE rates shown are for all AEs, regardless of whether or not they were treatment related, except for COMBI-d, for which rates of treatment-related events were reported.
[b]Grade 4 events occurred in 3 patients: thrombocytopenia, febrile neutropenia, and hypokalemia. A grade 5 event occurred in 1 patient: bile duct adenocarcinoma.
[c]A grade 4 event occurred in 1 patient: pancytopenia.
[d]Grade 5 events occurred in 3 patients (<1%): acute coronary syndrome, cerebral ischemia, and pleural infection (n=1 each).
[e]Grade 5 events occurred in 3 patients (<1%): cerebral hemorrhage (n=2) and brain stem hemorrhage (n=1).
[f]One patient experienced a grade 4 adverse event of this type.
[g]Grade 5 events occurred in 3 patients (1.3%): fatigue (and progressive disease; n=1), cardiac failure (n=1), and pulmonary embolism (n=1).
[h]Grade 5 events occurred in 6 patients (2.3%): fatigue and asthenia (n=1), cardiac arrest (n=1), cerebral hemorrhage (and progressive disease, n=1), hemiparesis (and progressive disease, n=1), pneumonia (n=1), and not specified (n=1).

Other Targeted Therapies: Imatinib

KIT (commonly known as *c-KIT*) mutations have been associated most commonly with mucosal and acral subtypes of melanoma.[22] Phase II studies testing imatinib, an inhibitor of mutated c-*KIT*, in patients with *KIT*-mutated or *KIT*-amplified metastatic melanomas demonstrated 20% to 30% overall response rate and 35% to 55% disease control rate.[96-98] Unfortunately, most of these responses were of limited duration. These phase II studies included a significant portion of patients with non-cutaneous melanoma (46%–71% mucosal). The results show trends toward better response in mucosal melanoma compared with acral/CSD subtypes, and toward better response for patients with *KIT* mutations versus amplifications alone.[97,98] Like BRAF inhibitors, patient selection by molecular screening is essential to identify patients who might potentially benefit; previous studies on unselected patients yielded no meaningful responses.[577,578]

Biochemotherapy

Biochemotherapy is the combination of chemotherapy and biological agents. In phase II-III trials, biochemotherapy (dacarbazine or temozolomide, cisplatin, and vinblastine or nitrosourea, plus IFN-alfa and IL-2) produced overall response rates of 21% to 64% and CR rates of 7.5% to 21% in patients with metastatic melanoma.[579-589] A small phase III randomized trial comparing sequential biochemotherapy (dacarbazine, cisplatin, and vinblastine [CVD] with IL-2 and IFN administered on a distinct schedule) with CVD showed biochemotherapy improved response rates (48% vs. 25%) and survival (median 11.9 months vs. 9.2 months).[590] In a phase III randomized intergroup trial (E3695), biochemotherapy (CVD plus IL-2 and IFN alpha-2b) produced a slightly higher response rate and progression free-survival than CVD alone, but it was not associated with either improved quality of response or OS, and was substantially more toxic.[591] Biochemotherapy should not be administered in centers that do not have substantial clinical experience and infrastructure to manage toxicities. Additional attempts to decrease toxicity of biochemotherapy by administering subcutaneous outpatient IL-2 did not show a substantial benefit of biochemotherapy versus chemotherapy alone.[585,592,593] A meta-analysis also showed that although biochemotherapy improved overall response rates, there was no survival benefit for patients with metastatic melanoma.[594]

Interleukin-2

High-dose IL-2 has been used extensively to treat metastatic melanoma in first-line and second-line settings. Although overall response rates are modest (<20%), those that achieve a complete response (<10%)

tend to have extremely durable responses and high rates of long-term survival [595-597] Thus, although median OS is usually 11 to 12 months, approximately 10% of patients achieve long-term survival (>5 years).[595,597-599] In one retrospective analysis of 305 patients who received IL-2 monotherapy for previously treated measurable metastatic disease, complete response was achieved in 4%, with median duration of response >176 months (range, 12 months to >253 months).[595] Of the 12 patients with CR, 10 survived at least 13 years.

High-dose IL-2 is associated with significant toxicities. Safe and effective administration requires careful selection of patients, close monitoring, and adherence to administration and AE management protocols.[600] High-dose IL-2 therapy should be restricted to institutions with medical staff experienced in the administration and management of these regimens.

Cytotoxic Therapy

Common cytotoxic agents being used in patients with metastatic melanoma include dacarbazine,[601,602] temozolomide,[595-597,602,603] and paclitaxel with or without carboplatin.[604-608] These have demonstrated modest response rates less than 20% in first-line and second-line settings.

Traditional paclitaxel formulation is solvent-based. Albumin-bound paclitaxel, also known as *nab*-paclitaxel, is a solvent-free formulation bound by stable albumin particles that has lower toxicity and higher bioavailability. This formulation yielded response rates of 22% to 26% in phase II trials among chemotherapy-naïve patients with metastatic melanoma.[609,610]

Little consensus exists regarding optimal standard chemotherapy for patients with metastatic melanoma, which most likely reflects the low level of activity of older FDA-approved agents.[611,612]

Palliative Radiation Therapy

Contrary to common perception that melanoma is radio-resistant, radiation often achieves palliation of symptomatic metastatic disease.[613-615] Clinically significant regression of radiated lesions of up to 60% has been reported in carefully-selected patients.[616,617]

SRS is gaining importance in the management of CNS metastases from melanoma. Retrospective studies have shown 1-year local tumor control rates from 72% to 100% for patients with limited CNS disease, but lower rates for patients with multiple or large (>2 cm) tumors.[618-623] With the increasing use of stereotactic radiation, the value of WBRT in patients with melanoma brain metastases is increasingly unclear and controversial. Virtually all the information available about the impact of RT for melanoma brain metastases comes from retrospective studies. It is almost impossible to separate out the impact of patient selection from the effect of treatment. Results from recent retrospective studies comparing patients who received SRS versus those who received WBRT are especially compromised by selection bias because WBRT is more likely to be used in patients with more extensive disease.[623,624] In clinical practice, the use of SRS in patients with a limited number of small brain tumors is gaining wider acceptance because studies have demonstrated late adverse effects of WBRT on cognitive function.[407,625-627] Prospective randomized studies are needed to determine the best approach to radiation for melanoma brain tumors.

Combining Radiation with Systemic Therapy

Some systemic therapy regimens may increase toxicity when given concurrently with radiation. A number of case studies have reported that

BRAF inhibitors vemurafenib and dabrafenib have radiosensitizing effects,[628-636] and a retrospective analysis by Hecht and colleagues[637] found that 57% of 70 patients receiving concomitant therapy experienced acute or late toxicities. Case reports indicate that radiosensitization reactions can also occur in patients treated with RT and subsequent BRAF inhibition.[634-636] Radiodermatitis was the most common of these toxicities, with acute events (grade ≥2) occurring in 36% of patients treated with concomitant RT plus dabrafenib or vemurafenib.[637] Acute dermatitis has also been reported in patients treated with WBRT and BRAF inhibitor therapy (either concurrent or sequential).[632,633] In the retrospective study by Hecht and colleagues,[637] BRAF inhibitor therapy was associated with increased risk of acute dermatitis among patients treated with WBRT (44% vs. 8%; $P = .07$). In contrast, a retrospective study by Gaudy-Marqueste and colleagues[638] found no evidence of radiodermatitis in 30 patients who received SRS and BRAF inhibitor therapy. A variety of other toxicities have been reported to be associated with RT plus BRAF inhibitor treatment; those reported in more than one patient include follicular cystic proliferation (13%), hearing disorder (4%), and dysphagia (2%).

Results from retrospective studies suggest that for patients with metastatic melanoma (including brain metastases), combining checkpoint immunotherapy (ipilimumab or nivolumab) with radiation of CNS or non-CNS metastases does not significantly increase the risk of toxicity.[139,639-645] However, multiple retrospective studies on ipilimumab and one on nivolumab failed to show that adding checkpoint immunotherapy provided additional clinical benefit in patients receiving RT for brain metastases, at least in terms of response rates and OS.[139,639,640,643,646] Several analyses found that concurrent or close proximity of RT and systemic therapy treatment improved response rates and OS, although results are inconsistent regarding the optimal order of administration.[639,641,644,647] Abscopal responses in non-irradiated tumors have been observed, but prospective trials are needed to confirm these effects because the delayed kinetics of ipilimumab response complicate interpretation of retrospective data.[641,648-650]

NCCN Recommendations

Multidisciplinary tumor board consultation is encouraged for patients with stage IV metastatic melanoma. Treatment depends on whether disease is limited (resectable) or disseminated (unresectable) as outlined below.

Resection, if feasible, is recommended for limited metastatic disease. In selected patients with a solitary site of visceral metastatic melanoma, a short period of observation or systemic treatment followed by repeat scans may be appropriate to rule out the possibility that the visceral metastasis is the first of many metastatic sites, and to better select patients for surgical intervention. Following observation or treatment, patients with resectable solitary sites of disease should be reassessed for surgery. If completely resected, patients with no evidence of disease (NED) can be observed or offered adjuvant treatment on clinical trial. There is panel consensus that adjuvant IFN alpha monotherapy outside of a clinical trial is inappropriate for resected stage IV disease. Alternatively, limited metastatic disease can be treated with systemic therapy either in the context of a clinical trial (preferred) or as a standard of care. Residual disease following incomplete resection for limited metastases is treated as described below for disseminated disease.

Disseminated disease can be managed by systemic therapy, clinical trial, intralesional injection with T-VEC, or best supportive care (see the NCCN Guidelines for Palliative Care). In addition, symptomatic patients

may receive palliative resection and/or radiation. A number of options are available for systemic therapy.

First-line Systemic Therapy

For first-line therapy of unresectable or metastatic disease, recommended treatment options include checkpoint immunotherapy, BRAF-targeted therapy for patients with *BRAF*-mutated disease, or clinical trial.

Checkpoint immunotherapy options in this setting include anti-PD-1 monotherapy with pembrolizumab (category 2A) or nivolumab (category 1) or nivolumab/ipilimumab combination therapy (category 2A). Checkpoint inhibitors have been shown to be effective regardless of *BRAF* mutation status. The NCCN Panel considers all recommended checkpoint immunotherapy options appropriate for both *BRAF* mutant and *BRAF* wild-type metastatic disease. There is interest in PD-L1 as a predictive biomarker for response to anti-PD-1 therapy, but to date it has not been discriminant enough to be used to inform treatment decisions in clinical practice.

Although ipilimumab is FDA approved for treatment of unresectable or metastatic melanoma, including both treatment-naïve and previously treated disease, single-agent ipilimumab monotherapy is no longer an NCCN-recommended first-line therapy option due results from the CheckMate 067 phase III trial showing improved outcomes with anti-PD-1 monotherapy or nivolumab/ipilimumab combination therapy compared with ipilimumab monotherapy.

Selection between Anti-PD-1 monotherapy and nivolumab/ipilimumab combination therapy should be informed by the consideration that although combination therapy has been shown to provide somewhat better PFS, it is associated with a much higher risk of serious immune-mediated toxicities. Treatment selection should therefore be informed by consideration of the patient's overall health, medical history, concomitant therapies, comorbidities, and compliance with proactive monitoring and management of AEs.

For patients with *BRAF*-mutant metastatic disease, BRAF-targeted therapy first-line options include BRAF/MEK inhibitor combination therapy with dabrafenib/trametinib or vemurafenib/cobimetinib, or single-agent BRAF inhibitor therapy with vemurafenib or dabrafenib. All of these regimens are category 1 based on results from phase 3 trials in the first-line setting (ie, BRIM-3, BREAK-3, COMBI-d, COMBI-v, CoBRIM). Both vemurafenib and dabrafenib are FDA approved as single-agent therapy for treatment of patients with metastatic or unresectable melanoma with *BRAF* V600E mutation as detected by an FDA-approved test.[651,652] Dabrafenib/trametinib and vemurafenib/cobimetinib combination therapy regimens are FDA approved for the treatment of patients with unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations, as detected by and FDA-approved test.[652-654] The Cobas 4800 *BRAF* V600 mutation test, a test for detecting the *BRAF* V600E mutation, received FDA approval as a companion diagnostic for selecting patients for treatment with vemurafenib. The THxID BRAF Kit, a test for detecting *BRAF* V600E or V600K mutations, received FDA approval as a companion diagnostic for selection of patients for treatment with dabrafenib and trametinib. The NCCN Panel recommends that *BRAF* mutational status should be tested using an FDA-approved test or by a facility approved by Clinical Laboratory Improvement Amendments (CLIA). The NCCN panel recommends that tissue for genetic analysis be obtained from either biopsy of a metastasis (preferred) or from archival material. The NCCN panel considers single-agent BRAF inhibitor monotherapy and BRAF/MEK inhibitor combination therapy as appropriate treatment

options for metastatic disease with any type of activating *BRAF* mutation (includes V600E, V600K, V600R, V600D, and others). Although trametinib is FDA approved for single-agent use to treat patients with unresectable or metastatic melanoma with *BRAF* V600E mutation,[654] trametinib monotherapy is no longer an NCCN-recommended treatment option due to relatively poor efficacy compared with BRAF inhibitor monotherapy and BRAF/MEK inhibitor combination therapy. Among the recommended BRAF-targeted therapy options, the BRAF/MEK inhibitor combination is preferred over BRAF inhibitor monotherapy based on results from phase III trials in the first-line setting showing improved outcomes and similar risk of toxicity (COMBI-d, COMBI-v, and CoBRIM).

For patients with documented *BRAF* V600 mutations, selection between first-line checkpoint immunotherapy and BRAF-targeted therapy can be difficult given the lack of comparative phase III clinical trials. Clinical trials are underway to address unanswered questions regarding the optimal sequencing and/or combination of these agents. The recommendation for first-line systemic therapy should be informed by the tempo of disease, and the presence or absence of cancer-related symptoms. Given that responses to checkpoint immunotherapy can take longer to develop, BRAF-targeted therapy may be preferred in cases where the disease is symptomatic or rapidly progressing or the overall health of the patient appears to be deteriorating. Patients with low-volume, asymptomatic metastatic melanoma may be good candidates for checkpoint immunotherapy, as there may be time for a durable antitumor immune response to emerge. Safety profiles and AE management approaches differ significantly for BRAF-targeted therapy versus checkpoint immunotherapy; treatment selection should therefore be informed by consideration of the patient's overall health, medical history, concomitant therapies, comorbidities, and compliance.

Second-line or Subsequent Therapy

For patients who progress on first-line therapy or achieve maximum clinical benefit from BRAF-targeted therapy (if *BRAF* mutated), options for second-line therapy depend on ECOG performance status. Patients with poor performance (PS 3-4) should be offered best supportive care. Patients with PS 0-2 have a variety of options depending on their *BRAF* status and treatment history. Based on the positive results from phase III trials supporting the recommended first-line therapies, these checkpoint immunotherapy and BRAF-targeted therapy regimens have been incorporated into the guidelines in the setting of second-line or subsequent therapy for qualifying patients: nivolumab, pembrolizumab, nivolumab/ipilimumab combination, dabrafenib, vemurafenib, dabrafenib/trametinib, or vemurafenib/cobimetinib combination. Due to lack of phase III trial data in patients with previously treated metastatic disease, however, these regimens are category 2A (rather than category 1) recommended options for second-line or subsequent systemic therapy. As described in previous sections, results from phase II or phase IV trials in patients with previously-treated advanced disease support second-line or subsequent systemic therapy for some of these options (eg, vemurafenib, dabrafenib, pembrolizumab).

In addition to the checkpoint immunotherapy regimens recommended for first-line, second-line, and subsequent treatment of metastatic disease, single-agent ipilimumab is an option in patients who have received prior systemic therapy for metastatic disease. This recommendation is based on the results from the pivotal phase III trial (CA184-002) in patients with previously-treated unresectable stage III or stage IV melanoma.

Of the recommended options for second-line and subsequent therapy, the NCCN panel recommends considering only those agents that are not the same or of the same class as agents the patient received

previously. Patients treated with ipilimumab who experience stable disease of three months' duration after week 12 of induction or partial response or CR, who subsequently experience progression of melanoma, may be offered re-induction with up to four doses of ipilimumab at 3 mg/kg every three weeks. Although anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab, pembrolizumab) agents are both checkpoint immunotherapies, they are not considered the same class of agent because they target different molecules. For patients who previously received ipilimumab, subsequent treatment with anti-PD-1 therapy is a recommended option, and vice versa. Patients who previously progressed or achieved maximal response on BRAF inhibitor therapy are unlikely to benefit from BRAF/MEK inhibitor combination therapy. Likewise, patients who progressed or achieved maximal response on BRAF/MEK inhibitor combination therapy are unlikely to respond to BRAF inhibitor monotherapy or to a different BRAF/MEK inhibitor combination. For patients who have progressed on checkpoint immunotherapies (and BRAF-targeted therapy if *BRAF* mutated), additional options to consider for second-line or subsequent therapy include high-dose IL-2, biochemotherapy (category 2B), cytotoxic agents, and imatinib for tumors with activating mutations of c-*KIT*. It is not known which of these options may provide benefit, as data supporting these approaches largely predate the development checkpoint inhibitor and BRAF-targeted therapies.

Immune Checkpoint Inhibitor Administration

Ipilimumab is FDA approved for treatment of unresectable or metastatic melanoma at a dose of 3 mg/kg of body weight, administered every 3 weeks for a total of 4 doses, consistent with the dosing regimen in the phase III trials described.[381] NCCN Member Institutions recommend the use of ipilimumab at the FDA-approved dose and schedule.

As described above, FDA-recommended dosing regimens indicate that treatment should continue until disease progression or unacceptable toxicity for all 3 of the approved regimens containing anti-PD-1 agents: nivolumab, pembrolizumab, and nivolumab/ipilimumab combination therapy. Due to the lack of data with long-term anti-PD-1 treatment, the optimal treatment duration is unknown. In the absence of unacceptable toxicity, it is common practice to continue anti-PD-1 therapy until maximal response. Although there is no standard definition for maximal response, it is commonly defined as no additional tumor regression on at least 2 consecutive scans taken at least 12 weeks apart. Treatment after maximal response is controversial. Continuing anti-PD-1 treatment for one 12-week cycle after maximal response has been achieved is not uncommon in clinical practice. NCCN-recommended dosing regimens are listed in Table 20.

Table 20. NCCN Recommended Dosing Regimens

Therapy	Recommended Regimen
Ipilimumab	3 mg/kg Q3W for up to 4 doses
Nivolumab monotherapy	3 mg/kg Q2W for up to 2 years
Nivolumab combination therapy (with ipilimumab)	1 mg/kg Q3W for 4 doses, then 3 mg/kg Q2W for up to 2 years
Pembrolizumab	2 mg/kg Q3W for up to 2 years

Safety

Management of Immune-related Toxicities

Much of the management of irAEs has evolved in centers using these agents in the context of clinical trials. As such, the following recommendations for management of irAEs represent a consensus of experienced experts rather than evidence-based guidelines.

Treatment-related AEs occur in a high percentage of patients treated with anti-CTLA-4 or anti-PD-1 agents, and grade 3-4 related AEs occur

in as many as 20% of patients receiving single-agent therapy and in ~50% receiving ipilimumab monotherapy or nivolumab/ipilimumab combination therapy. Careful selection of patients and AE monitoring and management are therefore critical to safe administration of all of these agents. Among other factors, patient selection should take into consideration age, comorbidities (eg, disease processes whose manifestations might be confused with immune-related toxicities), concomitant medications (eg, immunosuppressive therapies), and overall performance status. Patients with underlying autoimmune disorders are generally excluded from treatment with checkpoint immunotherapies.

The product labels for ipilimumab, nivolumab, and pembrolizumab provide specific guidelines for monitoring and management of irAEs.[381,526,527] Clinicians need to educate themselves about the pattern of toxicities and recognition of these toxicities, as well as management strategies. Formal training programs are strongly recommended, along with careful and frequent consultation of 1) the relevant package inserts; 2) other FDA-approved materials with detailed descriptions of the signs and symptoms of irAEs associated with ipilimumab and detailed protocols for management; and 3) standard institutional protocols for monitoring and managing irAEs.[381,655]

There are two broad categories of irAE monitoring and management: one for ipilimumab-containing regimens and one for anti-PD-1 monotherapy.

Ipilimumab-containing Regimens

Close monitoring of potentially lethal irAEs in patients receiving ipilimumab is essential.[538] In addition to proactive questioning of symptoms, patient and nursing education and frequent communication with the care team are essential for identifying and effectively managing irAEs.

A recommended management approach for many moderate to severe irAEs is withholding or discontinuing treatment and administering systemic corticosteroids. Diarrhea is the most common grade 3-4 irAE associated with checkpoint immunotherapy; severe cases were treated by high-dose corticosteroids. For severe enterocolitis that does not respond to systemic corticosteroids (within 1 week), the NCCN panel recommends infliximab 5 mg/kg; a single dose is sufficient to resolve severe colitis in most patients.[381,526,547 Merrill, 2014 #1858,548,549,561-563] Budesonide is not recommended for prophylactic treatment of enterocolitis. Infliximab may be used as a second-line approach for managing other types of severe steroid-refractory irAEs. For severe hepatotoxicity refractory to high-dose corticosteroids, the addition of mycophenolate is recommended instead of infliximab. This recommendation is based on the concern for possible hepatotoxicity from infliximab.[656] While patients are on combination agent immune suppression therapy (eg, prednisone plus mycophenolate), they may be at risk for opportunistic infection, and should be considered for pneumocystis prophylaxis (See NCCN Guidelines for Cancer-Associated Infections, INF-6). Immune-mediated dermatitis sometimes responds to topical corticosteroids, but systemic steroids may be needed for reactions that do not respond to topical application.[526] The NCCN panel also recommends referral or consultation with a dermatologist or provider experienced in cutaneous irAEs.

Endocrinopathies often require hormone replacement therapy, even after corticosteroids have been tapered off.[341,381,383,499,512,526,527,544] Clinicians should actively screen for symptoms of hypophysitis because the signs are subtle, often presenting as headache or asthenia.

Anti-PD-1 Monotherapy

AE monitoring and management for patients receiving anti-PD-1 monotherapy is similar to that for ipilimumab-containing regimens. As noted above, the frequency of grade 3-4 AEs requiring management is lower with anti-PD-1 monotherapy compared with ipilimumab-containing regimens. For patients with preexistent hypophysitis due to ipilimumab, anti-PD-1 therapy may be administered if patients are on appropriate physiologic replacement endocrine therapy.

Management of BRAF Inhibitor Toxicities

For patients on BRAF inhibitor therapy, the panel recommends regular dermatologic evaluation with referral to a dermatologist to monitor for skin complications. Although dabrafenib is not associated with significant photosensitivity, regular skin evaluation and referral to a dermatologist is still recommended as secondary skin lesions can develop. Fever is common in patients receiving dabrafenib and should be managed by treatment discontinuation and use of anti-pyretics such as acetaminophen and/or NSAIDs. After resolution of fever, resumption of dabrafenib or dabrafenib/trametinib at reduced dose may be tried. Patients treated by vemurafenib or dabrafenib should also be educated to report joint pain and swelling.

Management of Interleukin-2 and Biochemotherapy Toxicities

Caution is warranted in the administration of high-dose IL-2 or biochemotherapy due to the high degree of toxicity reported. Some patients may attempt biochemotherapy for palliation or to achieve a response that may render them eligible for other therapies. In any case, if such therapy is considered, the NCCN panel recommends patients to receive treatment at institutions with relevant expertise. Contraindications for IL-2 include inadequate organ reserve, poor performance status, and untreated or active brain involvement. Additionally, panelists raised concerns over potential synergistic toxicities between ipilimumab and high-dose IL-2 therapy, especially in the gastrointestinal tract.

Treatment of Patients with Brain Metastases

For patients with brain metastases, treatment of the CNS disease usually takes priority in an effort to delay or prevent intratumoral hemorrhage, seizures, or neurologic dysfunction. Treatment of melanoma brain metastases is based on symptoms, number of lesions present, and location of the lesions, as described in the NCCN Guidelines for Central Nervous System Cancers. SRS and/or WBRT may be administered either as the primary treatment or as an adjuvant following surgical resection. Compared with WBRT, SRS may have better long-term safety and allow earlier documentation of stable CNS disease, thus allowing earlier access to systemic agents and clinical trials that require stable CNS disease. For patients with *BRAF* mutation who present with systemic and CNS disease, BRAF or BRAF/MEK inhibitor systemic therapy is sometimes offered as first-line therapy, with radiation used as consolidation as needed. After treatment of the brain, options for management of extracranial sites are the same as for patients without brain metastases. Ipilimumab therapy is associated with the potential for long-term disease control outside the CNS.

In patients with both brain and extracranial metastases, systemic therapy may be administered during or after treatment of the CNS disease, with the exception of high-dose IL-2, which has low efficacy in patients with previously untreated brain metastases and which may worsen edema surrounding the untreated metastases. There is disagreement on the value of IL-2 therapy in patients with small brain metastases but no significant peritumoral edema; IL-2 may be considered in selected cases (category 2B). Interactions between RT and systemic therapies need to be very carefully considered as there is

potential for increased toxicity, particularly with concurrent or sequential BRAF-targeted therapy and radiation.

Follow-up

In the absence of clear data, opinions vary widely regarding the appropriate follow-up of patients with melanoma. There is debate about the appropriate surveillance methods and frequency of exams or other tests. As yet, there are no data to support that pre-symptomatic detection of visceral metastasis improves patient outcomes. While the obvious immediate clinical goal for ongoing surveillance of patients with NED is for identification of relapse or a second primary melanoma, it is important to consider the long-term impact of ongoing surveillance in terms of improved survival, patient quality of life, and exposure to risks associated with some surveillance methods.[657-659]

Surveillance Modalities

Modalities that have been tested for follow-up in melanoma patients include patient self-exam or reporting of symptoms, clinical physical exam, blood tests, and various imaging modalities (eg, chest x-ray, ultrasound, CT, PET/CT, MRI). The utility of these modalities has been evaluated in retrospective and observational studies terms of the proportion of lesions (recurrences and second primary melanomas) detected by the surveillance methods employed. These studies have shown that most recurrences are detected by the patient or during physical exam in the clinic. The proportion of recurrences detected by patients varies across studies (17%–67%), as does the proportion of recurrences detected by physician's physical exams (14%–55%), but clearly both of these modalities are essential for effective surveillance during follow-up.[660-666] Imaging tests detected 7% to 49% of recurrences.[126,660,662-666] Imaging methods that detected recurrences included CT scanning, lymph node ultrasound, chest x-ray, or abdominal ultrasound; detection by brain MRI or other imaging methods was rare.[660,662,664-666] Even in prospective trials where laboratory tests were conducted regularly, detection of recurrence by blood work results was extremely rare.[126,664]

Recurrences detected by patients or physician clinical exams are usually local, regional satellite or in-transit, or nodal, and less commonly distant.[126,664] Recurrences detected by imaging, on the other hand, are more likely distant and nodal; local or in-transit recurrences are rarely detected by imaging.[126,664] These findings, combined with the low percentage of recurrences identified by imaging some studies,[660,662,665,666] suggest that imaging can be used sparingly for surveillance, especially in patients who present with early-stage melanoma who are less likely to recur with systematic disease.

Imaging Methods: Sensitivity, Selectivity, and Safety

Studies on medical imaging have reported low yield, significant false positivity (often associated with increased patient anxiety and medical costs related to further work-up), and risks of cumulative radiation exposure.[657,658,667-673] A large meta-analysis compared ultrasound imaging, CT, PET, and PET/CT for the staging and surveillance of patients with melanoma.[134] Data from 74 studies containing 10,528 patients were included. For both staging and surveillance purposes, ultrasound was found to be associated with the highest sensitivity and specificity for lymph node metastases, while PET/CT was superior for detecting distant metastases. The safety of CT and PET/CT is a significant concern, however, because large population-based studies have shown that cumulative radiation exposure from repeated CT and nuclear imaging tests may be associated with an increased risk of cancer.[658,659,674]

Nodal basin ultrasound has emerged as a modality for surveillance in patients who are eligible for, but do not undergo, SLNB or in whom the procedure is not technically successful or feasible. Surveillance ultrasound is often used in patients with a positive sentinel node who have elected not to undergo CLND. This approach has been demonstrated to be safe in one prospective randomized trial that compared nodal basin ultrasound surveillance to CLND in patients with a positive sentinel node.[275] Results from a similar but much larger trial is eagerly awaited. [276]

Patterns of Recurrence

In order to design an efficient and effective follow-up schedule, the overall stage-specific risk of relapse, median time to initial relapse, and the likely location of recurrences must be understood.

Stage-specific Probability of Recurrence

The likelihood of recurrence is dependent on the stage of the primary disease at presentation. With increasing stage at first presentation, risk of recurrence increases and the distribution of recurrences changes.[126,661,664,675,676] Recurrence rates for completely excised melanoma in situ are sufficiently low that patients are considered cured following excision, with the exception that certain subtypes may recur locally (ie, lentigo maligna).[243,244,246,677]

For patients who present with stage I-II melanoma and who are rendered free of disease after initial treatment, recurrences are distributed as follows: approximately 15% to 20% are local or in/transit, ~50% in regional lymph nodes, and 29% at distant metastatic sites.[675,676] In patients who present with stage III melanoma, recurrences are more likely to be distant (~50%), with the remainder divided between local sites and regional lymph nodes.[126] Increasing stage III substage at initial presentation is associated with a greater proportion of distant recurrences.

Timing of Recurrence

In general, earlier stage melanoma recurs less often, but over a longer time period, while later stage melanoma recurs more often and over a shorter time period. For all stages of melanoma, the risk of recurrence generally decreases with time (from diagnosis), although it does not reach zero at any time.[126,661,662,664,676] Studies indicate that the risk of recurrence plateaus at between 2% to 5%.[126,661,678,679] Late recurrence (more than 10 years after diagnosis) is well documented, especially for patients initially presenting with early-stage melanoma.[678-680] Data from several studies suggest that the time it takes for the risk of recurrence to reach its low plateau depends on the stage of disease at first presentation. In a retrospective study of patients who initially presented with stage I melanoma (N = 1568), 80% of the 293 recurrences developed within the first 3 years, but some recurrences (<8%) were detected 5 to 10 years after the initial treatment.[661] A prospective study found that for patients with stage I or II at initial presentation, the risk of recurrence reached a low level by 4.4 years after initial diagnosis.[664] For patients initially presenting with stage III disease, the risk of recurrence reached low levels after only 2.7 years.[664] A retrospective study in patients initially presenting with stage III disease calculated the time until the risk of relapse dropped to 5% or less, and found that this time shortened as the substage at presentation increased (from stage IIIA to IIIC).[126] Recurrences to distant sites occur over a longer timeframe than local or regional recurrences, and all types of recurrence (local, regional, and distant) develop more quickly in patients who had more advanced disease at initial presentation.[126,676] Nonetheless, over 95% of observed regional nodal and distant recurrences were detected within 3

years for stage IIIA and IIIB melanoma, and within 2 years for IIIC melanoma.[126]

In summary, patients who have more advanced disease at first presentation are more likely recur, and will recur more quickly. Patients with less advanced disease at presentation are less likely to recur, and will recur more slowly, with especially long delays associated with development of recurrences at distant sites. In patients who have already had one recurrence, subsequent recurrences tend to occur at progressively shorter intervals.[676]

Risk of Developing a Second Primary Melanoma

Patients cured of an initial primary melanoma are at increased risk for developing a second primary melanoma. Although rates vary, most studies have reported that ~2% to 10% of patients with first primary melanomas develop second primary melanomas.[661,664,681-684] The risk of developing a second primary melanoma generally decreases with time from diagnosis of the first primary melanoma.[685] About one third of second primary melanomas are identified at the same time or within the first 3 months of the diagnosis of the first melanoma,[681] and about half are diagnosed within the first year.[682] For patients who have already developed 2 primary melanomas, the risk of developing a third is higher (16% by 1 year, 31% by 5 years).[682] Second primary melanomas are likely to occur at the same body region as the original lesion,[684] and are usually thinner than the original lesion,[682,686] possibly due to increased clinical surveillance. The probability of developing a second primary melanoma is increased by the presence of atypical/dysplastic nevi and a positive family history of melanoma.[682,686]

Long-term Impact of Surveillance

It is difficult to document the effect of intensive surveillance on the outcome of patients with melanoma. A structured follow-up program could permit the earlier detection of recurrent disease at a time when it might be more amenable to potentially curative treatment. This rationale for follow-up is particularly appropriate for patients at risk for a second primary melanoma, patients who have not undergone SLNB at risk for nodal recurrence, or in those patients with a positive sentinel node who elected not to undergo completion lymphadenectomy.

Several other reasons for a structured follow-up program include provision of ongoing psychosocial support, identification of familial kindreds, screening for second non-melanoma primary malignancies, patient education, and documentation of the results of treatment.[686-688]

Survival after Recurrence

Earlier detection of recurrence is assumed to be beneficial because lower tumor burden and younger age are associated with improved treatment response rates and survival. However, this concept has not been proven, even with the use of more effective therapies for advanced melanoma. Prospective randomized trials are needed to assess whether surveillance improves survival, and to determine the optimal frequency and duration of follow-up surveillance. In the absence of such trials, the patterns and risk factors of survival after recurrence can help inform design of appropriate surveillance schedules.

Risk Factors for Survival After Recurrence

Survival after recurrence is generally poor, and depends on the stage of disease at first presentation, site(s) of recurrence, stage of recurrence, disease-free interval, tumor thickness, ulceration, and response to initial therapy for the recurrence. [675,679,689-691] Survival nodal or distant metastatic recurrences also depend on the diameter of largest metastasis, number of metastases, and presence of visceral metastases.[675,690]

Patient Quality of Life and Emotional Well-Being

An additional consideration when designing a follow-up schedule is the impact of surveillance on the patient's quality life. Whereas normal exam results can have a positive effect on a patient's emotional well-being, follow-up visits can also cause stress associated with traveling to a clinic, the exam experience, and waiting for results. A meta-analysis of 15 studies reporting on psychosocial outcomes in patients with early stage (I/II) melanoma found that although anxiety with follow-up is common, patients value reassurance, information, and psychosocial support.[692] It was not uncommon for follow-up exams or imaging to be primarily motivated by patient request

Psychosocial support for patients not only impacts their quality of life, but may also impact clinical outcomes. Patients in one randomized study who participated in a structured psychiatric group intervention shortly after their diagnosis and initial surgical treatment showed a trend toward decreased recurrence and significantly better survival than those without the psychiatric group intervention.[687] Of note, improvement in active-behavioral coping over time was correlated with improved outcomes.

Patient Education

Skin cancer preventive education should be promoted for patients with melanoma and their families.[693,694] There is increasing evidence that regular sunscreen use may diminish the incidence of subsequent melanoma.[695] Patients can be made aware of the various resources that discuss skin cancer prevention. A list of useful resources is provided by the National Council on Skin Cancer Prevention at http://www.skincancerprevention.org/resources.

NCCN Recommendations

Follow-up recommendations described in this section are for surveillance for recurrence in patients with NED. Recommendations for assessment of disease response to therapy is described in the specific treatment sections or left to the discretion of the practitioner.

NCCN recommendations for follow-up are largely based on retrospective studies, generally well-accepted clinical practice, and panel consensus, and thus are not overly prescriptive. The panel felt that a recommendation for lifetime dermatologic surveillance for patients with melanoma at a frequency commensurate with risk is appropriate. Risk assessment should include likelihood of relapse, metastasis, or second primary melanoma or other skin cancer. Clinical discretion is recommended for determining the appropriate follow-up schedule on a case-by-case basis. The panel recommends the development of institutional protocols for follow-up, which can be consistent with the broad parameters of the guidelines despite differing between institutions due to institutional structure, resources and processes, and characteristics of the population served. As there is a lifetime increased risk of subsequent melanoma and non-melanoma skin cancers, lifelong dermatologic surveillance at a frequency consistent with risk is appropriate.

To balance cost with clinical efficacy, the follow-up schedule should depend on a variety of patient- and disease-specific factors associated with risk of recurrence, risk of second primary melanoma, and probability that the recurrence or second primary can be effectively treated. Although the optimal duration of follow-up remains controversial, it is probably not cost effective to follow all patients intensively for metastatic disease beyond five years.

It is important to highlight that most recurrences are detected through patient-reported symptoms and physician- or patient-reported physical exam findings, rather than by imaging surveillance. The follow-up schedule should consider the utility of these different surveillance methods in different settings. Whereas physical exam and recording of symptoms should be emphasized for patients who present with stage I/II melanoma, imaging may be incorporated into the follow-up of asymptomatic patients who present with more advanced disease or have other risk factors for recurrence.

Common Recommendations for All Patients

Skin examination and surveillance at least once a year for life is recommended for all patients with melanoma, including those who are rendered NED after treatment of stage 0, in situ melanoma. Annual exams should be conducted with care, as regular clinical examination has the highest diagnostic benefit; it is the most cost-effective method for early detection of treatable disease and provides additional diagnostic benefit by enabling imaging directed by symptoms or clinical findings. Patients with risk factors associated with increased risk of subsequent primary melanomas, such as prior multiple primary melanomas, family history of melanoma, and the presence of atypical/dysplastic nevi, should be enrolled in more intensive surveillance programs, and may benefit from adjuncts such as high-resolution total body photography. Coordination among the clinical team is recommended so that the yearly exam (and any further testing) is not duplicated across specialties. Clinicians should educate all patients about regular post-treatment self-exam of their skin and of their lymph nodes if they had stage IA to IV melanoma (and are NED).

Regional lymph node ultrasound may be considered for patients with an equivocal lymph node physical exam, patients who were offered but did not undergo SLNB, patients in whom SLNB was indicated but was not possible or not successful, or patients with a positive SLNB who did not undergo CLND. Nodal basin ultrasound is not a substitute for SLNB or CLND.

Routine blood testing to detect recurrence is not recommended. Appropriate workup, including radiologic imaging, should be promptly obtained in the setting of concerning signs and/or symptoms of recurrence.

Follow-up schedule should be tailored by risk of recurrence, prior primary melanoma, and family history of melanoma, and includes other factors such as atypical moles, moles/dysplastic nevi, and patient/physician concern.

Specific Recommendations

Stage IA-IIA

For patients with stage IA to IIA melanoma, a comprehensive H&P with specific emphasis on the regional nodes and skin should be performed every 6 to 12 months for five years and annually thereafter as clinically indicated. The consensus of the panel is that imaging to screen for asymptomatic recurrence/metastatic disease is not useful for these patients.

Stage IIB-IV

For patients with stage IIB-IV melanoma, a comprehensive H&P should be performed every 3 to 6 months for 2 years; then every 3 to 12 months for 3 years; and annually thereafter, as clinically indicated. Surveillance interval should be tailored to substage and based on assessment of risk factors for recurrence. In the absence of meaningful data on the association of rigorous routine surveillance imaging with improved long-term outcome for stage IIB-IIC, the recommendations remain controversial. Periodic surveillance CNS imaging for 3 years

might avert some of the substantial morbidity incurred by stage IIIC patients who present with symptomatic CNS recurrence. Brain MRI surveillance beyond three years, however, has low yield and therefore is less likely to be useful.

Although not recommended at baseline, in the absence of firm data, the panel acknowledged that surveillance chest x-ray, CT, brain MRI, and/or PET/CT every 3 to 12 months (unless otherwise mandated by clinical trial participation) could be considered to screen for recurrent disease at the discretion of the physician (category 2B). Because most recurrences manifest within the first 3 years (depending on stage and other risk factors), routine imaging to screen for asymptomatic recurrence is not recommended beyond 3 to 5 years.

Prior brain metastases increase risk of new brain metastases, and treatment success increases with decreasing brain tumor burden; therefore more frequent surveillance with brain MRI is recommended for these patients with prior brain metastases.

Tailoring the Follow-up Schedule: Key Considerations

The frequency of follow-up and intensity of cross-sectional imaging should be based on the conditional probability of recurrence at any point in time after the patient is rendered free of disease, as well as the options for treatment. Surveillance for patients at higher risk should be more frequent than for those at lower risk, especially for the first two years.

The intensity and interpretation of cross-sectional imaging should also be influenced by the potential for false positives, the desire to avoid unnecessary treatment, patient anxiety, the potential adverse effects of cumulative radiation exposure, and medical costs, as well as treatment options available in the event that asymptomatic recurrence is detected.

All of the available data on risk of recurrence, surveillance, and survival are based on patients treated in the era of older, generally ineffective chemotherapy, and not the current targeted therapies or checkpoint immunotherapies. Prospective analyses are necessary to determine whether the use of newer targeted therapies and immunotherapies will impact surveillance recommendations in asymptomatic high-risk patients.

Treatment of Recurrence

NCCN Recommendations

Persistent Disease or Local Scar Recurrence

The panel recognized the distinction between true local scar recurrence after inadequate initial excision (which most likely represents locally persistent disease) and local recurrence after adequate initial excision, (which likely represents dermal lymphatic disease appearing in proximity to the wide excision scar).[696] In the former situation, defined by the presence of in situ and/or radial growth phase, the prognosis after re-excision is related to the microstaging of the recurrence, whereas the latter scenario is prognostically similar to recurrent regional disease.

For persistent disease or true local scar recurrence after inadequate primary therapy, a biopsy is required for confirmation. Guidelines for this biopsy should be the same as for primary tumors. The workup should be similar to that of the primary tumor based on microstaging characteristics. Re-excision to appropriate margins is recommended, with or without lymphatic mapping and SLNB according to primary tumor characteristics. Adjuvant treatment should be based on pathologic stage of the recurrence, and should be similar to that of primary tumors of equivalent stage.

Local, Satellite, and/or In-Transit Recurrence

Initial clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Pathology should be confirmed by FNA cytology, if feasible, or core, incisional, or excisional biopsy. Local or satellite recurrences are in the deep dermis or subcutaneous fat within the melanoma scar or satellite metastasis adjacent to the melanoma scar. By definition they are recurrences after initial adequate wide excision, and lack in situ or radial growth phase. Tissue from the recurrence (preferred) or archival tissue should be assessed for mutation status if the patient is being considered for targeted therapy or enrollment in a clinical trial that includes mutation status as an eligibility criterion. Baseline imaging (CT and/or PET/CT or MRI) is recommended for staging and to evaluate specific signs or symptoms (category 2B).

Participation in a clinical trial should be considered in all cases of local, satellite, or in-transit recurrence. In the absence of extra-regional disease, complete surgical excision to clear margins is recommended whenever feasible. Lymphatic mapping with SLNB may be considered in patients with resectable in-transit disease on an individual basis (category 2B). The prognostic significance of a positive SLNB in patients with established local regional recurrence is unclear.

Options for treatment of unresectable local, satellite, or in-transit recurrences include intralesional injection with T-VEC, ILP or ILIwith melphalan, or systemic therapy (as recommended for metastatic disease). The following are category 2B alternatives: intralesional injections with BCG, IFN alfa, or IL-2, topical imiquimod (for superficial dermal lesions), local ablation therapy, or RT.

After CR to any of these modalities, options include participation in a clinical trial or observation. For those rendered free of disease by surgery, an additional adjuvant therapy option is high-dose IFN alfa (category 2B).

Regional Nodal Recurrence

For patients presenting with regional nodal recurrence, the clinical diagnosis should be confirmed by FNA (preferred) or core, incisional, or excisional biopsy. Tissue from the recurrence (preferred) or archival tissue should be assessed for mutation status if the patient is being considered for targeted therapy or enrollment in a clinical trial that includes mutation status as an eligibility criterion. Baseline imaging (CT and/or PET/CT or MRI) is recommended for staging and to evaluate specific signs or symptoms (category 2B).

For patients who have not undergone prior lymph node dissection or had an incomplete lymph node dissection, a CLND is advised. If the patient underwent a previous CLND, excision of the recurrence to negative margins is recommended if possible. After complete resection of nodal recurrence, options for adjuvant treatment include a clinical trial, observation, or, in patients who were not previously treated, high-dose or pegylated IFN alfa, high-dose ipilimumab (category 2B), or biochemotherapy (category 2B). Adjuvant radiation to the nodal basin may also be considered in selected high-risk patients based on size, location, and number of involved nodes, and/or macroscopic extranodal extension (category 2B). For patients with incompletely resected nodal recurrence, unresectable disease, or systemic disease, options include systemic therapy (preferred), clinical trial, palliative RT, intralesional injection with T-VEC, or best supportive care (see NCCN Guidelines for Palliative Care).

Distant Recurrence

For patients presenting with distant recurrence, the workup and treatment options are similar to those outlined previously for patients presenting initially with stage IV metastatic disease.

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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