National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Melanoma: Cutaneous

Version 2.2021 — February 19, 2021

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***Susan M. Swetter, MD/Chair** ϖ
Stanford Cancer Institute

***John A. Thompson, MD ‡ †/Vice-Chair**
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Mark R. Albertini, MD †
University of Wisconsin Carbone Cancer Center

Christopher A. Barker, MD §
Memorial Sloan Kettering Cancer Center

Joel Baumgartner, MD ¶
UC San Diego Moores Cancer Center

Genevieve Boland, MD, PhD ¶
Massachusetts General Hospital Cancer Center

Bartosz Chmielowski, MD, PhD ‡ †
UCLA Jonsson Comprehensive Cancer Center

Dominick DiMaio, MD ≠
Fred & Pamela Buffett Cancer Center

Alison Durham, MD ϖ
University of Michigan Rogel Cancer Center

Ryan C. Fields, MD ¶
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Martin D. Fleming, MD ¶
The University of Tennessee Health Science Center

Anjela Galan, MD ≠
Yale Cancer Center/ Smilow Cancer Hospital

Brian Gastman, MD ¶
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Kenneth Grossmann, MD, PhD †
Huntsman Cancer Institute at the University of Utah

Samantha Guild ¥
AIM at Melanoma

Ashley Holder, MD ¶
O'Neal Comprehensive Cancer Center at UAB

Douglas Johnson, MD †
Vanderbilt-Ingram Cancer Center

Richard W. Joseph, MD ‡ †
Mayo Clinic Cancer Center

Giorgos Karakousis, MD ¶
Abramson Cancer Center at the University of Pennsylvania

Kari Kendra, MD
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Julie R. Lange, MD, ScM ¶
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Ryan Lanning, MD, PhD §
University of Colorado Cancer Center

Kim Margolin, MD †
City of Hope National Medical Center

Anthony J. Olszanski, MD, RPh †
Fox Chase Cancer Center

Patrick A. Ott, MD, PhD † ‡ Þ
Dana-Farber/Brigham and Women's Cancer Center

Merrick I. Ross, MD ¶
The University of Texas MD Anderson Cancer Center

April K. Salama, MD †
Duke Cancer Institute

Rohit Sharma, MD ¶
UT Southwestern Simmons Comprehensive Cancer Center

Joseph Skitzki, MD ¶
Roswell Park Cancer Institute

Jeffrey Sosman, MD ‡
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Evan Wuthrick, MD §
Moffitt Cancer Center

NCCN
Anita Engh, PhD
Nicole McMillian, MS

Continue

[NCCN Guidelines Panel Disclosures]

ϖ Dermatology
‡ Hematology/ Hematology oncology
Þ Internal medicine
† Medical oncology
≠ Pathology
¥ Patient advocacy
§ Radiotherapy/ Radiation oncology
¶ Surgery/Surgical oncology
* Writing committee member

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Clinical Trials: NCCN believes that the best management for any patient with cancer 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/member_institutions.aspx.

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates to Version 2.2021 of the NCCN Guidelines for Cutaneous Melanoma from Version 1.2021 include:

ME-6
- Footnote mm revised: "...For patients with unresectable nodal disease, consider treatment with systemic therapy (options shown on ME-I) followed by resection, or treat as stage IV (ME-16). *Prospective trials supporting the systemic therapy options on ME-I included only a small subset of patients with stage III disease (unresectable).*" (Also for ME-14A, ME-15A)

ME-7A
- New footnotes regarding systemic therapy for Stage III (clinical satellite/in-transit) were added:
  - Footnote ss: *For low-volume in-transit disease, the high risk of toxicities associated with certain combination regimens may outweigh the benefit.* (Also for ME-13A)
  - Footnote tt: *Prospective trials supporting the systemic therapy options on ME-I included only a small subset of patients with stage III disease.* (Also for ME-13A, ME-15A)

ME-E Principles of Surgical Margins for Wide Excision of Primary Melanoma
- New references were added.

ME-I Systemic Therapy for Metastatic or Unresectable Disease
1 of 8
- First-line Therapy; Other recommended regimens
  - Revised: Combination targeted therapy and ~~anti-PD-L1 therapy~~ *immunotherapy* if BRAF V600-activating mutation present
    - ◊ *Dabrafenib/trametinib + pembrolizumab* was added as a category 2B recommendation with corresponding footnote m: *The triplet of dabrafenib, trametinib, and pembrolizumab was associated with longer median PFS and 24-month PFS compared to the doublet of dabrafenib and trametinib; however, grade 3–5 treatment-related adverse events occurred in 58% of patients (including one death from pneumonitis) in the triplet arm and 25% of patients in the doublet arm.*

5 of 8 References
- References were updated to include a section for *Dabrafenib/trametinib + pembrolizumab*
  - *Ferrucci PF, Di Giacomo AM, Del Vecchio M, et al. KEYNOTE-022 part 3: a randomized, double-blind, phase 2 study of pembrolizumab, dabrafenib, and trametinib in BRAF-mutant melanoma. J ImmunoTherapy Cancer;2020;8:e001806.*
  - *Ascierto PA, Ferrucci PF, Fisher R, et al. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. Nat Med 2019;25:941-946.*

Continued
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Updates to Version 1.2021 of the NCCN Guidelines for Cutaneous Melanoma from Version 3.2020 include:

General Changes

- **The Guideline name changed from "Cutaneous Melanoma" to "*Melanoma: Cutaneous.*"**

ME-1A

- **Footnote d revised: ~~Prognostic gene expression profiling (GEP) to differentiate melanomas at low versus high risk for metastasis may provide information on individual risk of recurrence, as an adjunct to standard AJCC staging. However, the currently available prognostic molecular techniques should not replace pathologic staging procedures, and the use of GEP testing according to specific melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients.~~**
  The use of gene expression profiling (GEP) testing according to specific AJCC-8 melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Moreover, since there is a low probability of metastasis in stage I melanoma and higher proportion of false-positive results, GEP testing should not guide clinical decision-making in this subgroup. **See Principles of Molecular Testing (ME-C).**
  (Also for ME-2A, ME-3)
- **Footnote e revised: "...not recommended for patients with cutaneous melanoma ~~who are without evidence of disease (NED)~~, unless required to guide adjuvant or other systemic therapy or consideration of clinical trials." (Also for ME-2A, ME-3)**
- **Footnote "f" is new: *Dermal-based melanomas that lack epidermal involvement or regression of the epidermal/junctional component and histologically simulate cutaneous or in-transit metastasis should undergo a thorough discussion to consider a dermal primary versus metastatic process. Baseline metastatic workup with imaging (CT chest/abdomen/pelvis or PET/CT) may be warranted to exclude stage III/IV disease at the outset.***
- **Footnote h revised: "~~Microsatellitosis is defined in the CAP 2016 melanoma protocol (version 3.4.0.0) 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." The presence of microsatellitosis is associated with higher~~ *Microsatellitosis represents microscopically identified lymphatic metastasis and confers an increased* risk of recurrence.**
  ***Microsatellites are found discontinuous from the primary tumor (adjacent or deep)*. The AJCC Cancer Staging Manual, Eighth Edition (2017) ~~no longer~~ *does not* defines microsatellitosis according to tumor nest dimension or distance from the primary tumor...." (Also for ME-4A)**
- **Footnote k revised: ~~In patients with pure desmoplastic melanoma, sentinel lymph node positivity is less common compared to conventional melanoma subtypes. Variability across studies in the rate of sentinel lymph node positivity in desmoplastic melanoma may be due to lack of standardized criteria for defining pure desmoplastic melanoma. In the setting of these conflicting reports, the role of SLNB in patients with pure desmoplastic melanoma remains controversial~~.**
  In patients with pure desmoplastic melanoma (>90% of invasive melanoma associated with prominent stromal fibrosis), sentinel lymph node biopsy (SLNB) positivity is less common compared to mixed desmoplastic/nondesmoplastic and conventional melanoma subtypes. Variability across studies in the rate of SLNB positivity in desmoplastic melanoma may be due to lack of standardized criteria for defining pure desmoplastic melanoma, histopathologic reproducibility, and/or reporting. In the setting of these conflicting reports, the role of SLNB in patients with pure desmoplastic melanoma remains controversial.
  (Also for 2A, ME-3)

ME-2

- **Clinical Stage: Revised, Stage IA *(T1a)* (<0.8 mm thick, no ulceration)**

ME-2A

- **Footnote l revised: "...or T1a lesions with Breslow depth <0.8 mm and with other adverse features (eg, ~~very high~~ mitotic index ~~≥2/mm²~~ *>2/mm²* [particularly in the setting of young age], lymphovascular invasion, combination of these factors)."**
- **Footnote n revised: "...~~Abnormalities~~ *Abnormal* or suspicious ~~lesions~~ *findings* on nodal basin US should..." (Also for ME-3, ME-4A)**

ME-3

- **Clinical Stage: Revised, Stage IB (T2a) or II *(T2b or higher)* ~~(>1 mm thick, N0)~~**

Continued
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ME-4
- "Microscopic satellites in biopsy specimen from primary lesion" pathway; Workup: Second bullet revised, ~~Consider~~ *Recommend* imaging for baseline staging.
- Microscopic satellites in wide excision specimen and sentinel node negative or SLNB not performed..." pathway
  - Workup
    - The following bullets were added:
      - *H&P*
      - *Routine lab tests not recommended*
      - *Recommend imaging for baseline staging*
      - *Imaging to evaluate specific signs or symptoms*
      - *BRAF* mutation testing if considering *adjuvant therapy or* clinical trial.
  - After Workup, new recommendation added: "*Consider delayed SLNB if not previously performed*" with bifurcation for "Sentinel node positive" and "*Sentinel node nedgative or SLNB not performed*."
- Footnote x was moved so that it applies to all patients in both of the top two pathways

ME-4A
- Footnote x revised to include references: *(Bartlett EK. J Surg Oncol 2019;119:200-207; Karakousis GC, et al. Ann Surg Oncol 2019;26:33-41.)*

ME-5A
- Footnote aa revised: "*BRAF* mutation testing is recommended for patients with stage III *melanoma* ~~at high risk for recurrence~~ for whom..."
- Footnote bb revised: "... Nodal basin US surveillance may not be preferred over ~~therapeutic~~ *completion* lymph node dissection in all cases (eg, patient preference due to the logistics of surveillance, *or when primary tumor histology and SLN tumor burden suggest a higher likelihood of additional regional nodal involvement*)..."
- Footnote cc revised: "...prospective randomized trials (MSLT-II and DeCOG~~: at least~~*; ie,* every 4 months during the first 2 years, then every 6 months during years 3 through 5*)*."

ME-6
- Workup: First bullet revised, Core biopsy or FNA ~~preferred~~ if feasible. If needle biopsy is not possible, ~~incisional or~~ excisional biopsy is acceptable. (Also for ME-7)
- New footnote ll added: *BRAF mutation testing is recommended for patients with stage III melanoma for whom future BRAF-directed therapy may be an option. See Principles of Molecular Testing (ME-C). Consider broader genomic profiling if the test results might guide further treatment decisions or eligibility for participation in a clinical trial.* (Also for ME-7)

ME-7
- Stage III (clinical satellite/in-transit), Initial Treatment of Unresectable disease; Local therapy options: Under "Intralesional injection options," revised, "~~BCG or~~ IL-2 (~~all~~ category 2B)" (Also for ME-13)

ME-7A
- Footnote ww is new: *Definitive or palliative RT can be considered for unresectable melanoma, depending on the goal of treatment. Definitive RT has the intent of durable irradiated tumor control. Palliative RT has the intent of relieving symptoms caused by tumor*. (Also for ME-13A)

ME-8
- Footnote zz revised: "... Biopsy techniques may include *core (preferred)*, FNA, ~~core,~~ incisional/*partial,* or excisional..." (Also for ME-9, ME-10, ME-12, ME-13A, ME-14A, ME-16A)

ME-10
- Stage IIB–IV NED; Follow-up: Last bullet revised, Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended after *3*–5 years*, depending on risk of relapse*.

Continued
UPDATES

ME-11 Common Follow-up Recommendations for All Patients

- Second bullet revised: ~~Pre-diagnostic clinical modalities (ie, total-body photography *and* sequential digital dermoscopy), and other imaging technologies (eg, reflectance confocal microscopy, electrical impedance spectroscopy) may enhance early detection of new primary melanoma in patients with high mole count and/or presence of clinically atypical nevi. The clinical utility of novel/emerging diagnostic imaging and molecular technologies (eg, noninvasive genomic patch testing) requires further investigation~~. *Available, noninvasive pre-biopsy imaging and molecular technologies have not been prospectively compared for diagnostic accuracy.* Pre-diagnostic clinical modalities (ie, total-body photography *and* sequential digital dermoscopy), and other imaging technologies (eg, reflectance confocal microscopy, electrical impedance spectroscopy) may enhance early detection of new primary melanoma in patients with high mole count and/or presence of clinically atypical nevi. *Pre-diagnostic noninvasive genomic patch testing may also be helpful to guide biopsy decisions*.
- Fifth bullet revised: "In patients with an equivocal lymph node exam, short-term follow-up *and/*or additional imaging (US *[preferred], or* CT ~~FDG PET/CT scan~~) should be considered, *with image-directed biopsy as warranted*."
- Seventh bullet revised: Follow-up schedule is influenced by risk of recurrence *and new*, ~~prior~~ primary melanoma, ~~and~~ *which depends on patient/*family history of melanoma, ~~and includes other factors such as~~ mole count, *and/or* presence of atypical moles/dysplastic nevi, ~~and patient/physician concern~~.
- Last bullet; Replaced the second arrow sub-bullet with the following:
  - *Multigene panel testing that includes CDKN2A is also recommended for patients with invasive cutaneous melanoma who have a first-degree relative diagnosed with pancreatic cancer* (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic).
  - Testing for other genes that can harbor melanoma-predisposing mutations ~~(eg, MC1R, CDK4, TERT, MITF, BRCA2, BAP1 [especially for uveal melanoma])~~ *(See Risk Factors for Melanoma Development (ME-A 1 of 2)* may be warranted.

ME-13A

- Footnote fff revised: "...In situations where adjuvant ipilimumab may be an option (eg, patients who progress during anti-PD-1 therapy with resectable disease), ~~it may be reasonable to use ipi3~~ *the recommended dose is 3 mg/kg*."

ME-14A

- Footnote iii revised: "...In situations where adjuvant ipilimumab may be an option (eg, patients who progress during anti-PD-1 therapy with resectable disease), ~~it may be reasonable to use ipi3~~ *the recommended dose is 3 mg/kg*." (Also for ME-15A)

ME-15A

- Footnote mm added: "*In patients with extensive resectable nodal disease at very high risk of recurrence after complete resection, or if resectability of nodal disease is uncertain, recommend multidisciplinary tumor board review to consider neoadjuvant systemic therapy, preferably in the context of a clinical trial. For patients with unresectable nodal disease, consider treatment with systemic therapy (options shown on ME-I) followed by resection, or treat as stage IV (ME-16).*"

ME-16 Distant metastatic disease

- Limited (Resectable) pathway: "Options" header changed to "*Adjuvant Treatment* Options."

ME-16A

- Footnote mmm revised: "...In situations where adjuvant ipilimumab may be an option (eg, patients who progress during anti-PD-1 therapy with resectable disease), ~~it may be reasonable to use ipi3~~ *the recommended dose is 3 mg/kg*."

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ME-A Risk Factors for Development of Single or Multiple Primary Melanomas

- Fifth bullet; Genetic predisposition
  - First arrow sub-bullet revised: Presence of germline mutations or polymorphisms predisposing to melanoma ~~(including~~ *eg,* CDKN2a, CDK4, MC1R, BRCA2, BAP1 [especially for uveal melanoma], *TERT, MITF, PTEN* and ~~potentially~~ *potential* other genes).
  - Second arrow sub-bullet revised: Family history of cutaneous melanoma (especially if multiple), pancreatic ~~cancer~~, *renal and/or breast cancer*, astrocytoma, uveal melanoma, and/or mesothelioma.
- New references added:
  - *Bubien V, Bonnet F, Brouste V, et al. High cumulative risks of cancer in patients with PTEN hamartoma tumour syndrome. J Med Genet 2013;50:255-263.*
  - *Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res 2012;18:400-407.*
  - *Leachman SA, Lucero OM, Sampson JE, et al. Identification, genetic testing, and management of hereditary melanoma. Cancer Metastasis Rev 2017;36:77-90.*

ME-B Principles of Biopsy of a Suspicious Pigmented Lesion 1 of 3

- First bullet revised: "Excisional/*complete* biopsy (elliptical, punch..."
- Third bullet revised: "...However, a broad shave biopsy may be optimal for histologic assessment for melanoma in situ (MIS), lentigo maligna (LM) type *(ie, melanoma on skin with high cumulative sun damage [CSD])*."
- Footnotes removed
  - If clinical evaluation of incisional biopsy suggests that microstaging is inadequate, consider narrow margin excisional biopsy.
  - For melanoma in situ (MIS), lentigo maligna type, a broad shave biopsy may help to optimize diagnostic sampling.

2 of 3 and 3 of 3 Principles of Pathology for Primary Melanoma

- This section was extensively revised.

ME-C Principles of Molecular Testing 1 of 7

- Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication
  - First Bullet; First arrow sub-bullet revised: "Melanocytic neoplasms of uncertain biologic potential present a unique challenge to pathologists and treating clinicians. ~~Ancillary methods to aid in benign versus malignant differentiation include molecular cytogenetics (eg, comparative genomic hybridization [CGH]), fluorescence in situ hybridization [FISH]), gene expression profiling (GEP), next-generation sequencing (NGS), and immunohistochemistry (IHC), among others. While limited reports on the intermediate category of melanocytic neoplasia show evolutionary pathogenic genetic alteration during melanoma progression,[4] there are insufficient data from histologically ambiguous melanocytic neoplasms. Because ancillary tests are intended as adjuncts, and not replacements, for clinician and expert dermatopathologist examination, they should always be interpreted within the context of the clinical and histopathologic findings~~. *Ancillary tests to differentiate benign from malignant melanocytic neoplasms include immunohistochemistry (IHC) and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), single-nucleotide polymorphism (SNP) array, and next-generation sequencing (NGS). These tests may facilitate interpretation of cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests should be used as adjuncts to clinical and expert dermatopathologic examination and therefore be interpreted within the context of these findings."*

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UPDATES

ME-C Principles of Molecular Testing (continued)
1 of 7
- **Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication**
  - **Second Bullet; Prognostic Testing; Arrow sub-bullets revised**
    - **"Commercially available GEP tests are marketed as being able to classify cutaneous melanoma into separate categories based on risk of metastasis. However, it remains unclear whether these ~~tests~~ *GEP platforms* provide clinically actionable prognostic information when used in addition to or in comparison with known clinicopathologic factors or multivariable nomograms that incorporate patient sex, age, tumor location and thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and SLNB status..."**
    - **"...It remains unclear whether ~~this GEP profile is~~ *available GEP platforms are* reliably predictive of outcome across the risk spectrum of melanoma..."**

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- **Biomarkers with potential utility for immune therapy; PD-L1 (Programmed Death-Ligand 1)**
  - **Under "IHC for PD-L1 may help identify patients more likely to respond to immune checkpoint inhibitors" revised: "*Testing for tumor PD-L1 should not guide clinical decision-making. The utility of this biomarker requires further investigation*."**

5 of 7
- **Reasons for retesting metastatic tissue; Last arrow sub-bullet revised: "~~Repeat testing upon recurrence or progression may be warranted if there are concerns about initial testing on primary tumors due to inadequate tissue or use of a less accurate testing platform (eg, IHC)~~.*While the V600E mutation is the most common BRAF mutation, other BRAF mutations exist that may respond equally well to BRAF inhibitors. Some tests have lower sensitivity/specificity or detect only particular mutations. If needed for clinical care, repeat testing using a different methodology may be warranted to detect non-V600E BRAF mutations, or other mutations in different genes. If the initially submitted tissue was of poor quality, a new biopsy may be required before repeat testing is ordered*."**
- **Molecular testing requirements; First arrow sub-bullet revised: "Use of a properly accredited laboratory (CLIA *or CAP*)"**

6 of 7 and 7 of 7
- **References updated**

ME-D Principles of Imaging
1 of 5
- **Under "Imaging modalities include": *Nodal basin US for regional lymph node assessment* was added.**

2 of 5
- **Workup: "Consider baseline brain imaging (MRI) in asymptomatic patients if adjuvant therapy is planned" was removed.**

4 of 5
- **Follow-up (surveillance for recurrence in patients with no evidence of disease)**
  - **Under first bullet; Arrow sub-bullets revised:**
    - **In patients with an equivocal lymph node exam, short-term follow-up *and/*or additional imaging (US *[preferred] or* CT, ~~FDG PET/CT scan~~) should be considered, *with imaging-directed biopsy as warranted.***
    - **New arrow sub-bullet added: *Where radiologic expertise is available, regional nodal US may be utilized in higher risk (eg, T3/T4) melanomas if SLNB is not performed or not technically feasible. Nodal basin US is not a substitute for SLNB.***
  - **Under Stage IIB–IV (NED): Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended after *3*–5 years, *depending on risk of relapse*.**

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ME-E Principles of Surgical Margins for Wide Excision of Primary Melanoma

- This page was extensively revised.

ME-F Principles of Sentinel Lymph Node Biopsy (SLNB)

1 of 3

- General Principles
  - Sixth bullet; Sub-bullets revised
    - "For patients with a melanoma Breslow depth of <0.8 mm without ulceration *(T1a)*, the probability of a positive SLN is less than 5%..."
    - "For patients with clinical stage IB, T1b melanoma (Breslow depth <0.8 mm with ulceration or 0.8–1 mm with or without ulceration), or T1a lesions with Breslow depth <0.8 mm and with other adverse features (eg, ~~very high~~ mitotic index ~~≥2/mm²~~ >2/mm^2 [particularly in the setting of young age]..."
    - "For patients with stage IB (T2a) or II *(T2b and higher) melanoma* ~~(>1 mm thick, any feature, N0)~~, the probability of a positive SLN is generally greater than 10%. However..."
    - New sub-bullet added: *Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Currently available GEP tests should not be used to determine SLNB eligibility*.

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- Principles of Pathology
  - Fourth bullet revised: In cases where the histologic findings in the SLN are equivocal, comparison of cytomorphology to that of the primary tumor, *additional immunohistochemistry staining for PRAME (for differentiation of nodal nevi vs. melanoma metastasis)* and/or consultation with an experienced dermatopathologist should be considered.
  - New bullet added: *Caution should be used when calling an SLN positive based solely upon immunohistochemistry staining of rare, small cells that lack cytomorphologic atypia. Positive staining of rare non-melanoma cells may be seen in lymph nodes with a variety of immunohistochemistry stains used to detect melanocytes. Correlation of the immunohistochemistry stain with the H&E slide is recommended. Additional H&E levels and immunohistochemistry stains may be useful*.
- New references added.

ME-G Principles of Completion/Therapeutic Lymph Node Dissection

- Adequacy of Regional Lymph Node Dissection
  - New bullets added:
    - For a positive Cloquet's node (as part of a superficial inguinal lymph node dissection), iliac and obturator lymph node dissection may be considered, but is not mandatory given the effectiveness of modern adjuvant therapy.
    - Therapeutic iliac and obturator lymph node dissection may be considered if imaging shows resectable lymphadenopathy.
  - Last bullet revised: "...a superficial parotidectomy *with facial nerve preservation* and appropriate neck dissection of the draining nodal basins is recommended."
  - Bullet removed: Iliac and obturator lymph node dissection should be considered if pelvic CT is positive (category 2A) or if Cloquet's node is positive (category 2B).
- Footnote b is new: *In patients with extensive resectable nodal disease at very high risk of recurrence after complete resection, or if resectability of nodal disease is uncertain, recommend multidisciplinary tumor board review to consider neoadjuvant systemic therapy, preferably in the context of a clinical trial. For patients with unresectable nodal disease, consider treatment with systemic therapy (options shown on ME-I) followed by resection, or treat as stage IV (ME-16)*.

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UPDATES

ME-H Principles of Radiation
1 of 7

- **Definitive Therapy; Sub-bullet revised: "Definitive radiation is ~~rarely used to treat an in situ melanoma (lentigo maligna). This~~ may be considered *as a treatment option for MIS, LM-type (ie, high-cumulative sun damage [CSD])* in medically inoperable patients or those in whom surgical morbidity of complete resection would be prohibitive.'**
- **Adjuvant Therapy**
  - **Bullet removed: Adjuvant radiation is not routinely recommended to the primary site based on low rates of local recurrence following surgical excision.**
- **Reference added.**

3 of 7

- **Distant Metastatic Disease; Brain Metastases**
  - **Revised: "*Palliative* whole brain RT (WBRT) ~~as primary treatment~~".**
    - **Sub-bullet revised: ~~Recent data from a randomized trial in patients with non-small cell lung cancer suggest that WBRT may not provide a clinically meaningful benefit beyond supportive measures in patients with a poor performance status and too many lesions for SRS/SRT or surgery~~. *Only consider for palliative purposes when SRS/SRT is not feasible in patients with good performance status for whom effective systemic therapy has failed (see ME-L)*.**
    - **Sub-bullets removed**
      - **Upfront WBRT is generally not recommended for metastatic melanoma, and SRS/SRT is the preferred strategy when feasible.**
      - **WBRT can be considered for selected patients with too many lesions for SRS and/or are symptomatic from intracranial tumor burden.**
  - **Revised: ~~WBRT as~~ Adjuvant *WBRT* ~~treatment (category 3)~~**
    - **The sub-bullets in this section were extensively revised and reorganized, including:**
      - **New sub-bullet added: *Adjuvant WBRT after resection or SRS/SRT is not recommended for patients with melanoma***
      - **Sub-bullets removed:**
        - **Adjuvant SRS/SRT is preferred over WBRT when feasible.**
        - **Adjuvant WBRT may be considered in uncommon circumstances where there is clinical concern for leptomeningeal spread and/or in situations where SRS/SRT is not technically feasible (ie, a patient who cannot undergo an MRI).**
      - **Sub-bullet "Common WBRT regimens include:" and its corresponding radiation dosing sub-bullets were removed and replaced with "*For dosing, see Palliative WBRT section.*"**

Continued
UPDATES

ME-I Systemic Therapy for Metastatic or Unresectable Disease
1 of 8

- **First-line therapy; Other recommended regimens**
  - ***Pembrolizumab/low-dose ipilimumab (category 2B)* added as an option with corresponding footnote "*Dosing used in KEYNOTE-029: Pembrolizumab 2 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks (Q3W) for four doses, followed by pembrolizumab 2 mg/kg Q3W for up to 2 years or disease progression, intolerable toxicity, withdrawal of consent, or investigator decision.*"**
- **Second-line or subsequent therapy; Systemic therapy; Preferred regimens**
  - ***Pembrolizumab/low-dose ipilimumab or tumors that have progressed after prior anti-PD-1 therapy* added as an option.**

2 of 8

- **Footnote d revised: See NCCN Guidelines for Management of Immunotherapy-Related Toxicities *for proactive monitoring and management of toxicities in patients undergoing treatment with immune checkpoint inhibitors*.**
- **Footnote e revised: ~~The use of PD-L1 as a biomarker for selection of anti-PD-1 therapy and/or nivolumab/ipilimumab combination therapy is an emerging research issue with non-uniform application among the NCCN Member Institutions (category 2B).~~ *Testing for tumor PD-L1 should not guide clinical decision-making. The utility of this biomarker requires further investigation*.**
- **Footnote f revised: "...absence of comorbidities or autoimmune processes that would elevate the risk of irAEs; *and* patient social support and anticipated compliance with medical team to handle toxicities*; ~~and absent/low tissue PD-L1~~*."**
- **Footnote j revised: If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF inhibitor monotherapy ~~with dabrafenib or vemurafenib recommended~~ *is an* option, especially in patients who are not appropriate candidates for checkpoint immunotherapy.**
- **Footnote m revised: "...For patients who progressed on single-agent anti-PD-1 checkpoint immunotherapy, ~~nivolumab/ipilimumab~~ *anti-PD-1/ipilimumab* combination therapy or ipilimumab monotherapy is a reasonable treatment option..."**

3 of 8 Other Systemic Therapies

- **Cytotoxic Therapy for Metastatic Disease (useful in certain circumstances)**
  - **Bullets revised**
    - ◊ **The literature is not directive regarding the specific chemotherapeutic agent(s), *and none of these regimens offers* superior outcomes, ~~and none of these regimens~~ *or has* been shown to improve OS in a randomized phase III trial setting. However, the literature does provide evidence that some patients ~~respond to~~ *experience tumor regression (usually temporary) after* cytotoxic therapy.**
    - ◊ **Cytotoxic agents that have been used alone or in combination ~~with some success~~ include (but are not limited to): dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, carboplatin/paclitaxel, and cisplatin/vinblastine/dacarbazine (CVD) (category 2B for CVD).**

5 of 8 References

- **References were updated.**

Continued
UPDATES

ME-J Systemic Therapy Considerations

1 of 4

- **Considerations for Selection of Systemic Therapy for Unresectable or Metastatic Disease**
  - **Considerations for anti-PD-1/ipilimumab dosing and anti-PD-1 monotherapy dosing**
    - ◊ **First sub-bullet revised: "The clinical response to *FDA-approved* ~~alternative~~ anti-PD-1 dosing schedules ~~(ie, every 2, 3, or 4 weeks)~~ appears similar, although comparative trials are not available..."**
    - ◊ **New bullet added: *The initial clinical trials and FDA approvals of pembrolizumab and nivolumab in 2014 used dosing based on patient weight (2 mg/kg every 3 weeks for pembrolizumab and 3 mg/kg every 2 weeks for nivolumab). Subsequently the FDA amended dosing to flat doses (200 mg or 400 mg every 3 or 6 weeks, respectively, for pembrolizumab, or 240 mg or 480 mg every 2 or 4 weeks, respectively, for nivolumab), which are safe and efficacious. However, substantial cost savings for pembrolizumab and nivolumab may be obtained by weight-based dosing, depending on patient weight and on institutional practices regarding vial sharing.***

2 of 4

- **Considerations for Patients with CNS Disease**
  - **Bullet removed: In patients with BRAF V600-mutated melanoma brain metastases, there are insufficient data to address whether immune therapy or BRAF/MEK inhibitor therapy is the preferred for first-line systemic therapy.**
- **When to Stop or Switch Therapies;**
  - **Definition of maximal clinical benefit; Sub-bullet revised: Most patients who achieve a complete *or partial* response and discontinue anti-PD-1 monotherapy after 2 years of therapy maintain the response with 2 years of follow-up.**

3 of 4

- **Recommendations for Patients Who Progress on Systemic Therapy**
  - ***BRAF* V600-activating mutation present**
    - ◊ **Under "For patients who progress on BRAF/MEK inhibitor combination therapy, anti-PD-1 therapy, and ipilimumab (in combination with anti-PD-1 or sequentially), consider the following options," new sub-bullet *High-dose bolus IL-2* added.**
  - **BRAF V600-activating mutation not present**
    - ◊ **Under "For patients with progression on anti-PD-1 and ipilimumab (in combination with anti-PD-1 or sequentially), consider the following options" new sub-bullet *High-dose bolus IL-2* added.**
  - **New section added: *Use of High-Dose IL-2 in Select Patients***
  - **New reference added: *Buchbinder EI, Dutcher JP, Daniels GA, et al. Therapy with high-dose Interleukin-2 (HD IL-2) in metastatic melanoma and renal cell carcinoma following PD1 or PDL1 inhibition. J Immunother Cancer 2019;7:49*.**

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- **Use of Cytotoxic Agents for Unresectable or Distant Metastatic Disease; Second bullet revised: ~~Recommended~~ *Considerations for* cytotoxic agents**
- **Considerations for Selection of Adjuvant Systemic Therapy**
  - **Considerations for selecting among adjuvant systemic therapies; Last sub-bullet revised: "Ipilimumab (3 mg/kg) i*s the recommended dose. This regimen* appears to result in a similar disease-free survival..."**

Continued

UPDATES

ME-K Management of Toxicities Associated with Targeted Therapy

- Targeted Therapy (BRAF or combined BRAF/MEK inhibitors)
  - Dermatologic: New sub-bullet added, *Severe skin toxicity (eg, drug-induced hypersensitivity syndrome) can occur with the use of BRAF inhibitors following immune checkpoint blockade, and requires prompt dermatologic consultation for accurate diagnosis and treatment*.
  - Pyrexia; Revised: "...Stopping or holding ~~dabrafenib and trametinib~~ *BRAF/MEK inhibitor combination* at the onset of pyrexia will often interrupt the episode, and treatment can be resumed with full-dose ~~dabrafenib and trametinib~~ *BRAF/MEK* inhibitors upon cessation of pyrexia and pyrexia-related symptoms. Upon re-exposure to ~~dabrafenib and trametinib~~ *BRAF/MEK inhibitors*, 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~~ *BRAF/MEK inhibitors*, 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."
  - Last bullet revised: "For more information on toxicities associated with dabrafenib with or without trametinib, ~~or~~ vemurafenib with or without cobimetinib, *or encorafenib with or without binimetinib* and for the management of these toxicities..."
- Footnote a is new: The frequency of pyrexia and other adverse events varies between specific BRAF/MEK inhibitor combinations.
- Reference added.

ME-L Principles of Brain Metastases Management
1 of 5

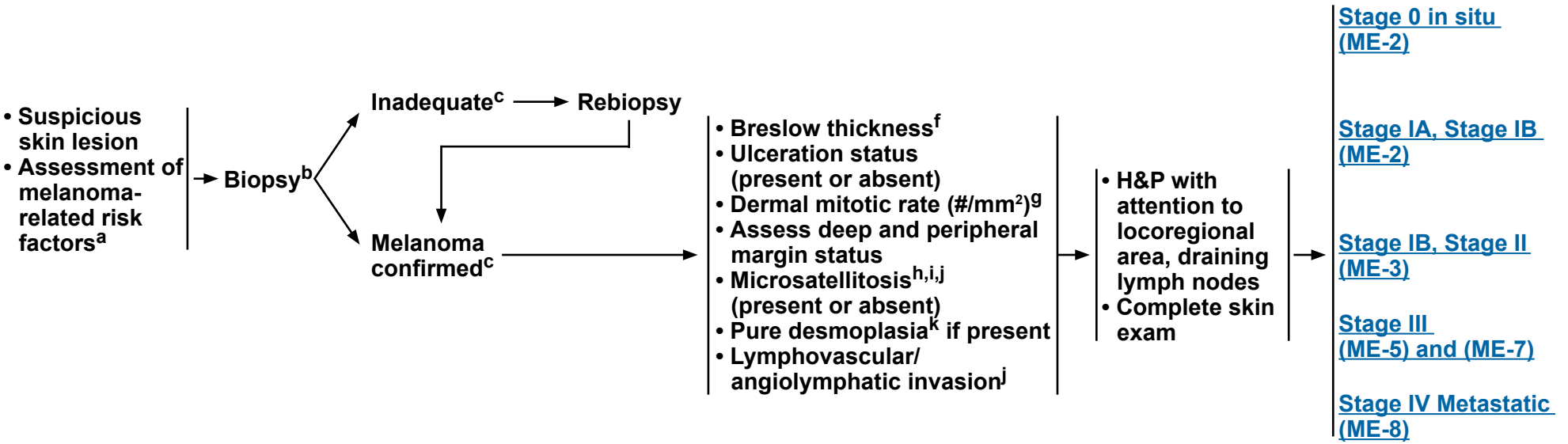
- Selection of Initial Treatment Modality (Brain-Directed vs. Systemic): Bullet revised and moved from the last bullet to the second bullet: As a general approach, patients who present with a higher burden of intracranial disease associated with symptoms will often require local management. In patients with lower volume, asymptomatic brain metastases as well as those with extensive extracranial disease, an initial course of systemic therapy may be preferred. *It is likely that many patients presenting with brain metastases will need both systemic therapy and local brain-directed therapy over their course of treatment*.

2 of 5

- Brain-Directed Therapy
  - Surgery versus radiation
    - ◊ First arrow sub-bullet; Second diamond sub-bullet revised: Adjuvant WBRT is not ~~generally~~ recommended *after resection for melanoma brain metastases*.
    - ◊ Second arrow sub-bullet; New diamond sub-bullet added: *Adjuvant WBRT is not recommended after SRS/SRT for melanoma brain metastases.*
    - ◊ Third arrow sub-bullet revised: *Palliative* WBRT ~~may be considered in symptomatic metastases not amenable to SRS. However, WBRT delivers a lower dose of radiation to metastases in the brain and is associated with lower local control and increased risk of late neurocognitive impairment~~.
      - – New diamond sub-bullets added:
        - ▪ Only recommended for palliative purposes when SRS/SRT is not feasible in patients with good performance status for whom effective systemic therapy has failed.
        - ▪ WBRT delivers a lower dose of radiation to metastases in the brain and is associated with lower local control and increased risk of lateneurocognitive impairment.
- Management of symptoms
  - Second arrow sub-bullet: Second diamond sub-bullet revised: "... due to the adverse side effect profile of medical therapies. *However, as hemorrhage is associated with increased risk of seizure, selected patients with large bleeding lesions could be considered for prophylactic anticonvulsants*."

3 of 5

- Systemic Therapy
  - Patients who are most likely to be considered for systemic therapy as the sole initial treatment modality include: Revised, "Patients with ~~small (~~<3 cm~~)~~ asymptomatic brain metastases, not requiring corticosteroids..."



See Footnotes on ME-1A

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

FOOTNOTES FOR CLINICAL PRESENTATION, PATHOLOGY REPORT, AND PRELIMINARY WORKUP

[a] See Risk Factors for Melanoma Development (ME-A).
[b] See Principles of Biopsy and Pathology (ME-B).
[c] If diagnostic biopsy is inadequate for treatment decisions, rebiopsy may be appropriate.
[d] The use of gene expression profiling (GEP) testing according to specific AJCC-8 melanoma stage (before or after sentinel lymph node biopsy [SLNB]) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Moreover, since there is a low probability of metastasis in stage I melanoma and a higher proportion of false-positive results, GEP testing should not guide clinical decision-making in this subgroup. See Principles of Molecular Testing (ME-C).
[e] Mutational analysis for *BRAF* or multigene testing of the primary lesion is not recommended for patients with cutaneous melanoma unless required to guide adjuvant or other systemic therapy or consideration of clinical trials. See Principles of Molecular Testing (ME-C).
[f] Dermal-based melanomas that lack epidermal involvement or regression of the epidermal/junctional component and histologically simulate cutaneous or in-transit metastasis should undergo a thorough discussion to consider a dermal primary versus metastatic process. Baseline metastatic workup with imaging (CT chest/abdomen/pelvis or PET/CT) may be warranted to exclude stage III/IV disease at the outset.
[g] Although dermal mitotic rate is no longer included in the determination of T1 staging in the AJCC Cancer Staging Manual, Eighth Edition (2017), it remains an important prognostic factor across all thickness categories and should be included in the pathology assessment of melanoma biopsies and surgical excisions.
[h] Microsatellitosis represents microscopically identified lymphatic metastasis and confers an increased risk of recurrence. Microsatellites are found discontinuous from the primary tumor (adjacent or deep). The AJCC Cancer Staging Manual, Eighth Edition (2017) does not define microsatellitosis according to tumor nest dimension or distance from the primary tumor. It classifies cases with microsatellites, clinical satellites, or in-transit metastases as N1c, N2c, or N3c based on the number of tumor-involved regional lymph nodes (0, 1, or ≥2, respectively).
[i] For patients with microsatellitosis in the biopsy specimen (and no clinical evidence of nodal/distant disease), see ME-4 for further workup and treatment.
[j] At times it may be difficult to distinguish whether invasive melanoma is present within a lymphatic channel or represents a microsatellite. In this instance, immunohistochemistry using a specific lymphatic marker such as D2-40 may assist in distinction.
[k] In patients with pure desmoplastic melanoma (>90% of invasive melanoma associated with prominent stromal fibrosis), SLNB positivity is less common compared to mixed desmoplastic/nondesmoplastic and conventional melanoma subtypes. Variability across studies in the rate of SLNB positivity in desmoplastic melanoma may be due to lack of standardized criteria for defining pure desmoplastic melanoma, histopathologic reproducibility, and/or reporting. In the setting of these conflicting reports, the role of SLNB in patients with pure desmoplastic melanoma remains controversial.

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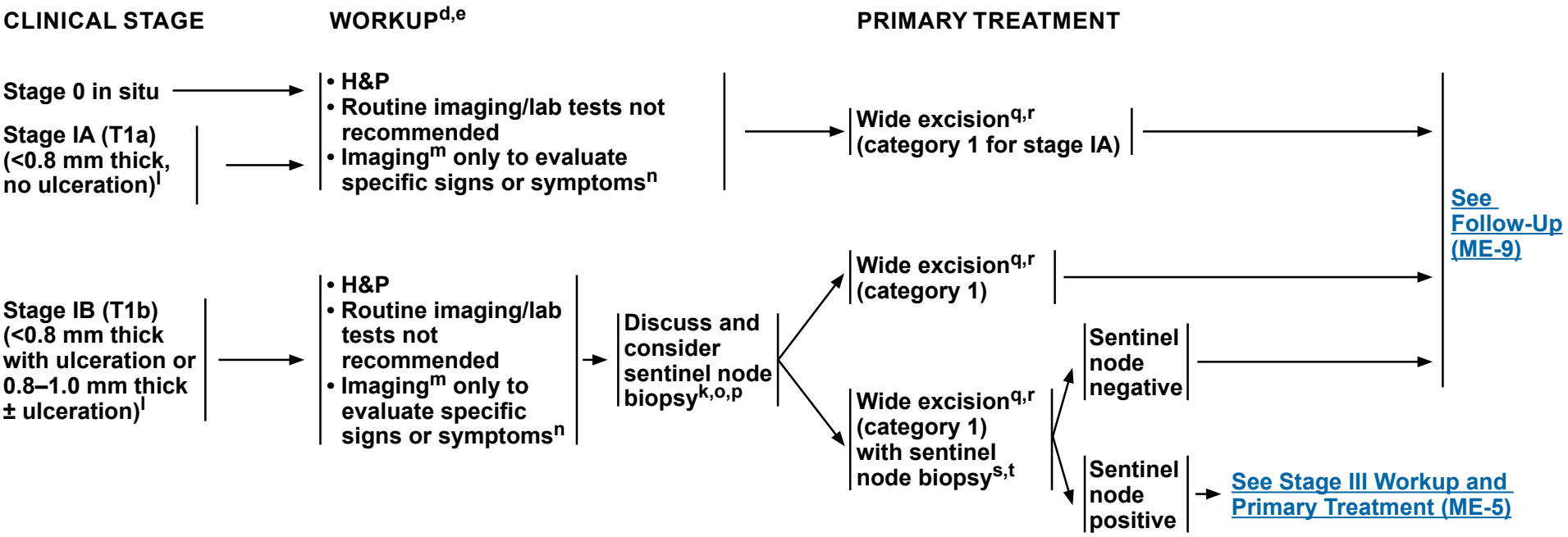

See other footnotes on ME-2A

[l]If a patient's risk of a positive sentinel lymph node (SLN) is <5%, NCCN does not recommend SLNB. This would include clinical stage IA, T1a melanoma with Breslow depth of <0.8 mm without ulceration, or other adverse features, unless there is significant uncertainty about the adequacy of microstaging (positive deep margins). If a patient's risk of a positive SLNB is 5%–10%, NCCN recommends discussing and considering SLNB. This would include clinical stage IB, T1b melanoma (Breslow depth <0.8 mm with ulceration or 0.8–1 mm with or without ulceration), or T1a lesions with Breslow depth <0.8 mm and with other adverse features (eg, mitotic index >2/mm^2 [particularly in the setting of young age], lymphovascular invasion, combination of these factors).

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FOOTNOTES FOR WORKUP AND PRIMARY TREATMENT

[d]The use of GEP testing according to specific AJCC-8 melanoma stage (before or after SLNB) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Moreover, since there is a low probability of metastasis in stage I melanoma and a higher proportion of false-positive results, GEP testing should not guide clinical decision-making in this subgroup. See Principles of Molecular Testing (ME-C).

[e]Mutational analysis for *BRAF* or multigene testing of the primary lesion is not recommended for patients with cutaneous melanoma unless required to guide adjuvant or other systemic therapy or consideration of clinical trials. See Principles of Molecular Testing (ME-C).

[k]In patients with pure desmoplastic melanoma (>90% of invasive melanoma associated with prominent stromal fibrosis), SLNB positivity is less common compared to mixed desmoplastic/nondesmoplastic and conventional melanoma subtypes. Variability across studies in the rate of SLNB positivity in desmoplastic melanoma may be due to lack of standardized criteria for defining pure desmoplastic melanoma, histopathologic reproducibility, and/or reporting. In the setting of these conflicting reports, the role of SLNB in patients with pure desmoplastic melanoma remains controversial.

[m]See Principles of Imaging–Workup (ME-D).

[n]Consider nodal basin ultrasound (US) prior to SLNB for melanoma patients with an equivocal regional lymph node physical exam. Abnormal or suspicious findings on nodal basin US should be confirmed histologically, whenever possible. Nodal basin US is not a substitute for SLNB. Negative nodal basin US is not a substitute for biopsy of clinically suspicious lymph nodes.

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

[p]SLNB is an important staging tool. While SLNB itself has not been shown to improve disease-specific survival (DSS), a positive SLNB would upstage a patient to stage III. Adjuvant therapy has been shown to improve recurrence-free survival (RFS) and overall survival (OS) in selected high-risk stage III patients.

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

[r]For patients with microsatellitosis in the wide excision specimen, see ME-4 for further workup and treatment.

[s]SLNs should be evaluated with serial sectioning and immunohistochemistry.

[t]See Principles of Sentinel Lymph Node Biopsy (SLNB) (ME-F).

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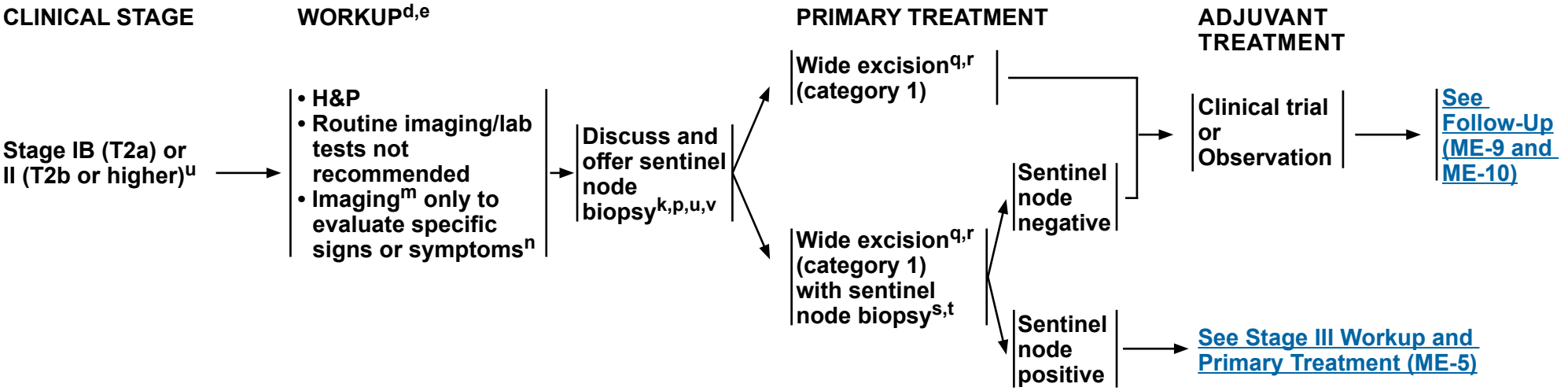

[u]Microsatellitosis, when present in the initial biopsy or wide excision specimen, defines at least N1c and at least stage IIIB disease. Although less well studied than other stage III patient populations, SLN status does have prognostic significance in patients with microsatellitosis, with a positive SLN upstaging a patient to at least N2c, stage IIIC. SLNB should be considered in patients with microsatellitosis, especially if it will alter management decisions.

[d]The use of GEP testing according to specific AJCC-8 melanoma stage (before or after SLNB) requires further prospective investigation in large, contemporary data sets of unselected patients. Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Moreover, since there is a low probability of metastasis in stage I melanoma and a higher proportion of false-positive results, GEP testing should not guide clinical decision-making in this subgroup.
See Principles of Molecular Testing (ME-C).

[e]Mutational analysis for *BRAF* or multigene testing of the primary lesion is not recommended for patients with cutaneous melanoma unless required to guide adjuvant or other systemic therapy or consideration of clinical trials. See Principles of Molecular Testing (ME-C).

[k]In patients with pure desmoplastic melanoma (>90% of invasive melanoma associated with prominent stromal fibrosis), SLNB positivity is less common compared to mixed desmoplastic/nondesmoplastic and conventional melanoma subtypes. Variability across studies in the rate of SLNB positivity in desmoplastic melanoma may be due to lack of standardized criteria for defining pure desmoplastic melanoma, histopathologic reproducibility, and/or reporting. In the setting of these conflicting reports, the role of SLNB in patients with pure desmoplastic melanoma remains controversial.

[m]See Principles of Imaging–Workup (ME-D).

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

[r]For patients with microsatellitosis in the wide excision specimen, see ME-4 for further workup and treatment.

[s]SLNs should be evaluated with serial sectioning and immunohistochemistry.

[t]See Principles of Sentinel Lymph Node Biopsy (SLNB) (ME-F).

[v]Decision not to perform SLNB may be based on significant patient comorbidities, patient preference, or other factors (such as advanced patient age). See Common Follow-up Recommendations for All Patients (ME-11).

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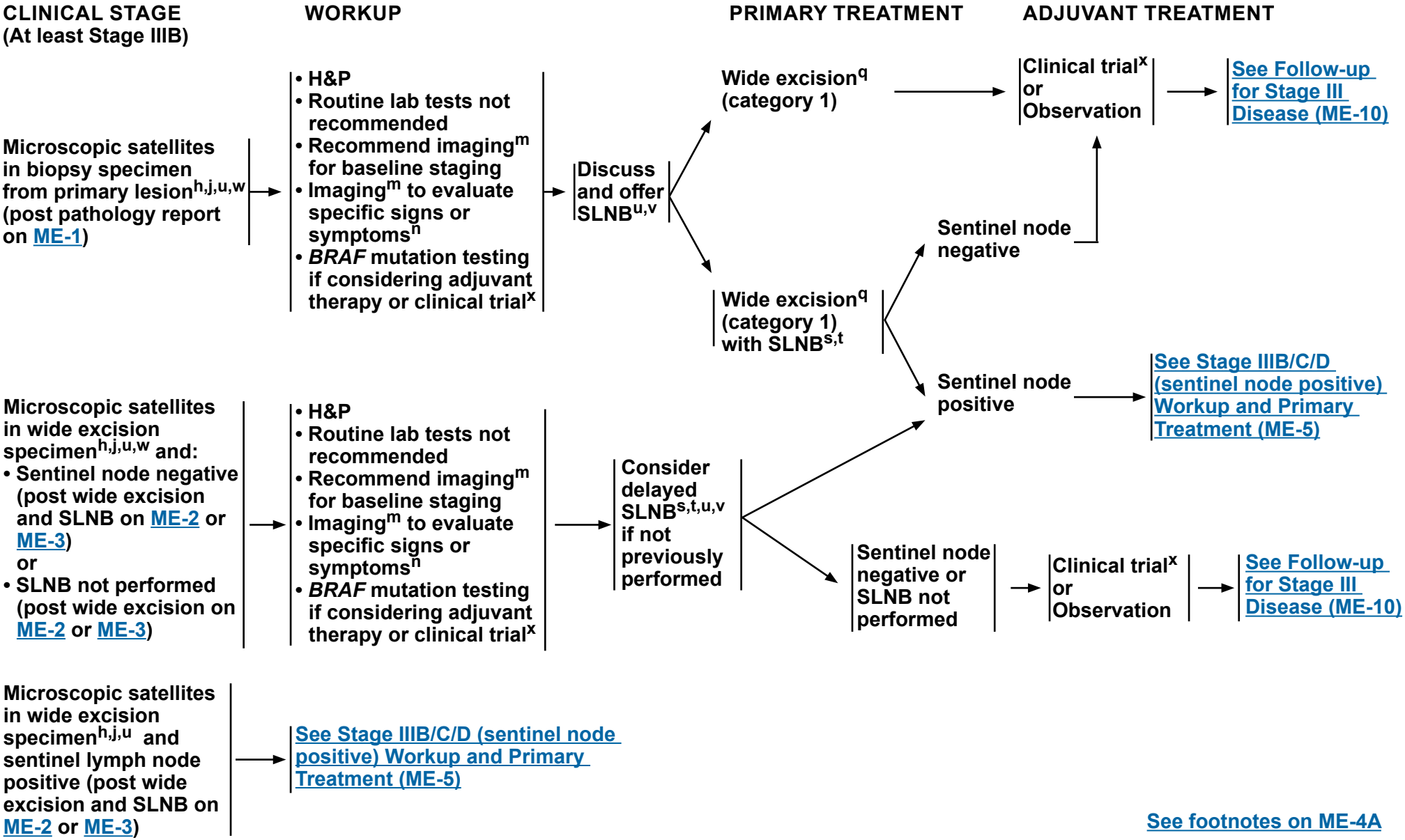

See footnotes on ME-4A

Note: All recommendations are category 2A unless otherwise indicated.
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FOOTNOTES FOR MICROSCOPIC SATELLITES

[h]Microsatellitosis represents microscopically identified lymphatic metastasis and confers an increased risk of recurrence. Microsatellites are found discontinuous from the primary tumor (adjacent or deep). The AJCC Cancer Staging Manual, Eighth Edition (2017) does not define microsatellitosis according to tumor nest dimension or distance from the primary tumor. It classifies cases with microsatellites, clinical satellites, or in-transit metastases as N1c, N2c, or N3c based on the number of tumor-involved regional lymph nodes (0, 1, or ≥2, respectively).

[j]At times it may be difficult to distinguish whether invasive melanoma is present within a lymphatic channel or represents a microsatellite. In this instance, immunohistochemistry using a specific lymphatic marker such as D2-40 may assist in distinction.

[m]See Principles of Imaging–Workup (ME-D).

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

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

[s]SLNs should be evaluated with serial sectioning and immunohistochemistry.

[t]See Principles of Sentinel Lymph Node Biopsy (SLNB) (ME-F).

[u]Microsatellitosis, when present in the initial biopsy or wide excision specimen, defines at least N1c and at least stage IIIB disease. Although less well studied than other stage III patient populations, SLN status does have prognostic significance in patients with microsatellitosis, with a positive SLN upstaging a patient to at least N2c, stage IIIC. SLNB should be considered in patients with microsatellitosis, especially if it will alter management decisions.

[v]Decision not to perform SLNB may be based on significant patient comorbidities, patient preference, or other factors (such as advanced patient age). See Common Follow-up Recommendations for All Patients (ME-11).

[w]Primary lesion microsatellitosis with no clinical satellite, in-transit, or nodal disease.

[x]Patients with stage IIIB melanoma based on microsatellites alone demonstrate more favorable survival compared with those with a positive SLNB. (Bartlett EK. J Surg Oncol 2019;119:200-207; Karakousis GC, et al. Ann Surg Oncol 2019;26:33-41.) Because SLN-negative, microsatellite-positive patients were not studied in adjuvant therapy trials, the results of these trials may not be applicable to this subgroup.

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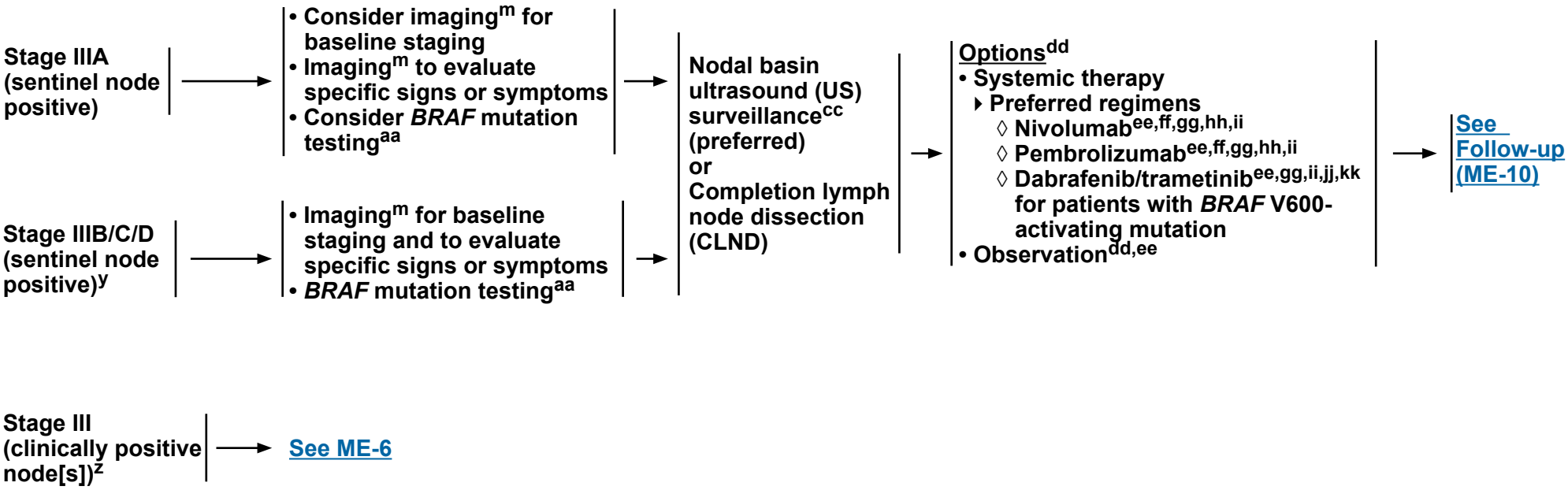

See footnotes on ME-5A

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FOOTNOTES FOR STAGE III (SENTINEL NODE POSITIVE)

[m]See Principles of Imaging–Workup (ME-D).

[y]For patients with a positive sentinel lymph node(s), the presence of microsatellites in the initial biopsy of the primary tumor or wide excision specimen will upstage the patient to at least IIIC. The increased risk of recurrence associated with the presence of microsatellitosis should be acknowledged in any discussion about adjuvant therapy, independent of the SLN tumor burden. Follow-up of patients with microsatellitosis should be more frequent, commensurate with their increased risk of recurrence.

[z]For patients with clinically positive node(s), the presence of microsatellites in the initial biopsy of the primary tumor or wide excision specimen upstages patients to a minimum of stage IIIC. While this does not change the recommended workup and treatment, it is associated with higher risk of recurrence when compared to patients without microsatellitosis.

[aa]*BRAF* mutation testing is recommended for patients with stage III melanoma for whom future *BRAF*-directed therapy may be an option.
See Principles of Molecular Testing (ME-C).

[bb]For patients with a positive sentinel node, two prospective randomized phase III studies have demonstrated no improvement in melanoma-specific survival or OS in patients undergoing CLND compared to those who underwent nodal basin US surveillance, although only one study (MSLT-II) included primary melanomas on the head and neck. CLND did provide additional prognostic information as well as improvement in regional control/recurrence at the expense of increased morbidity, including wound complications and long-term lymphedema. Factors that predict non-SLN positivity include sentinel node tumor burden, number of positive nodes, and thickness/ulceration of the primary tumor. Nodal basin US surveillance may not be preferred over CLND in all cases (eg, patient preference due to the logistics of surveillance, or when primary tumor histology and SLN tumor burden suggest a higher likelihood of additional regional nodal involvement).
See Principles of Completion/Therapeutic Lymph Node Dissection (ME-G).

[cc]For patients with a positive SLNB who do not undergo CLND, it would be appropriate for the frequency of clinical exam and US surveillance to be consistent with the two prospective randomized trials (MSLT-II and DeCOG; ie, every 4 months during the first 2 years, then every 6 months during years 3 through 5).

[dd]The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity. See Systemic Therapy Considerations (ME-J).

[ee]In patients with very-low-risk stage IIIA disease (non-ulcerated primary ≤2 mm thickness, SLN metastasis <1 mm), the toxicity of adjuvant therapy may outweigh the benefit.

[ff]Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported.

[gg]Adjuvant dabrafenib/trametinib and pembrolizumab are category 1 options for patients with AJCC 7th Edition stage IIIA with SLN metastasis >1 mm or stage IIIB/C disease. Adjuvant nivolumab is a category 1 option for patients with AJCC 7th Edition stage IIIB/C disease.

[hh]Randomized clinical trials testing adjuvant anti-PD-1 therapy included patients with sentinel node-positive disease at higher risk of recurrence: those with ulcerated primary (ie, nivolumab, pembrolizumab) or an SLN metastasis >1 mm (pembrolizumab).

[ii]All patients in the clinical trials studying adjuvant anti-PD-1 or adjuvant dabrafenib/trametinib were required to undergo CLND prior to randomization. In the setting of two prospective trials demonstrating that CLND has no impact on DSS or OS, it is unclear whether CLND should be a factor in the decision to use either adjuvant therapy in sentinel node-positive patients.

[jj]The randomized clinical trial testing adjuvant dabrafenib/trametinib combination therapy for patients with *BRAF* V600E/K mutation included patients with sentinel node-positive disease at higher risk of recurrence: those with ulcerated primary and/or SLN metastasis >1 mm.

[kk]In the event of unacceptable toxicities to dabrafenib/trametinib, other BRAF/MEK inhibitor combinations can be considered.

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CLINICAL/ PATHOLOGIC STAGE	WORKUP	PRIMARY TREATMENT	ADJUVANT TREATMENT
Stage III (clinically positive node[s])[z] →	• **Core biopsy or FNA if feasible. If needle biopsy is not possible, excisional biopsy is acceptable.** • **Imaging[m] for baseline staging and to evaluate specific signs or symptoms** • ***BRAF* mutation testing[ll]**	**Wide excision of primary tumor[q] (category 1)[z] + therapeutic lymph node dissection (TLND)[mm]** →	**Systemic therapy options:[dd]** • **Preferred regimens** ▸ **Nivolumab[ff] (category 1)** ▸ **Pembrolizumab[ff] (category 1)** ▸ **Dabrafenib/trametinib[kk] for patients with *BRAF* V600-activating mutation (category 1)** **and/or** **Locoregional therapy option:** • **Consider RT to nodal basin in selected high-risk patients based on location, size, and number of involved nodes, gross and/or histologic extracapsular extension[nn,oo] (category 2B)** **or** **Observation[dd]** →	**See Follow-up (ME-10)[y]**

[m] See Principles of Imaging–Workup (ME-D).

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

[z] For patients with clinically positive node(s), the presence of microsatellites in the initial biopsy of the primary tumor or wide excision specimen upstages patients to at least stage IIIC. While this does not change the recommended workup and treatment, it is associated with higher risk of recurrence when compared to patients without microsatellitosis.

[dd] The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity. See Systemic Therapy Considerations (ME-J).

[ff] Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported.

[kk] In the event of unacceptable toxicities to dabrafenib/trametinib, other BRAF/MEK inhibitor combinations can be considered.

[ll] *BRAF* mutation testing is recommended for patients with stage III melanoma for whom future *BRAF*-directed therapy may be an option. See Principles of Molecular Testing (ME-C). Consider broader genomic profiling if the test results might guide further treatment decisions or eligibility for participation in a clinical trial.

[mm] In patients with extensive resectable nodal disease at very high risk of recurrence after complete resection, or if resectability of nodal disease is uncertain, recommend multidisciplinary tumor board review to consider neoadjuvant systemic therapy, preferably in the context of a clinical trial. For patients with unresectable nodal disease, consider treatment with systemic therapy (options shown on ME-I) followed by resection, or treat as stage IV (ME-16). Prospective trials supporting the systemic therapy options on ME-I included only a small subset of patients with stage III disease (unresectable).

[nn] Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in RFS or OS. Its benefits must be weighed against potential toxicities such as lymphedema (limb) or oropharyngeal complications. The impact of these potential toxicities should be considered in the context of available systemic adjuvant treatment options.

[oo] See Principles of Radiation Therapy for Melanoma (ME-H).

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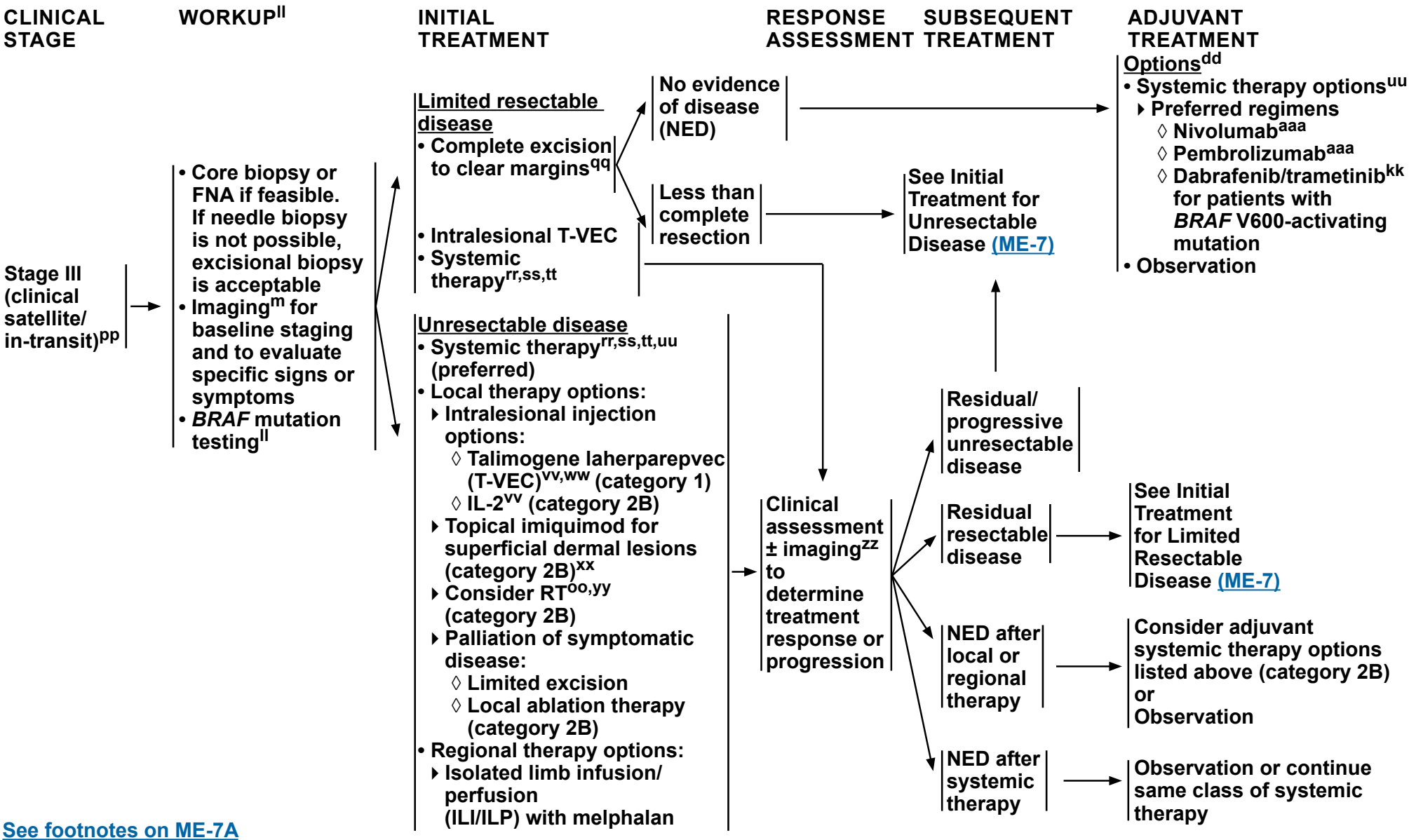


See footnotes on ME-7A

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

FOOTNOTES FOR STAGE III (CLINICAL SATELLITE/IN-TRANSIT)

[m]See Principles of Imaging–Workup (ME-D).

[ll]*BRAF* mutation testing is recommended for patients with stage III melanoma for whom future *BRAF*-directed therapy may be an option. See Principles of Molecular Testing (ME-C). Consider broader genomic profiling if the test results might guide further treatment decisions or eligibility for participation in a clinical trial.

[dd]The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity. See Systemic Therapy Considerations (ME-J).

[kk]In the event of unacceptable toxicities to dabrafenib/trametinib, other BRAF/MEK inhibitor combinations could be considered.

[oo]See Principles of Radiation Therapy for Melanoma (ME-H).

[pp]Intralymphatic metastases can be characterized as clinically or pathologically detectable satellite metastases (visible or microscopic cutaneous and/or subcutaneous metastases occurring within 2 cm of the primary melanoma), or in-transit metastases (regional cutaneous and/or subcutaneous metastases identified at a distance greater than 2 cm from the primary melanoma). The 2-cm cutoff is consistent with AJCC staging definitions. Satellite and in-transit metastases are biologically and prognostically similar.

[qq]Consider sentinel node biopsy for resectable clinical satellite/in-transit disease if it will change treatment options (category 2B). See Principles of Sentinel Lymph Node Biopsy (SLNB) (ME-F).

[rr]See Systemic Therapy for Metastatic or Unresectable Disease (ME-I).

[ss]For low-volume in-transit disease, the high risk of toxicities associated with certain combination regimens may outweigh the benefit.

[tt]Prospective trials supporting the systemic therapy options on ME-I included only a small subset of patients with stage III disease.

[uu]For patients who have previously received systemic therapy for cutaneous melanoma (either as active treatment or adjuvant therapy), selection of systemic therapy regimen should be informed by response to prior systemic therapies. For patients who experienced progression of melanoma during or shortly after a prior therapy, consider agents of a different class. For patients who experience disease control (CR, PR, or SD) on a prior systemic therapy, and have no residual toxicity, but subsequently experienced disease progression/relapse >3 months after treatment discontinuation, systemic therapy with the same agent or same class of agents may be considered.

[vv]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 AJCC 7th Edition stage IIIB and IIIC disease, and was more likely to be seen in patients who were treatment naive.

[ww]These options have been preference stratified as "Preferred Regimens."

[xx]These options have been preference stratified as "Useful In Certain Circumstances."

[yy]Definitive or palliative radiation therapy RT can be considered for unresectable melanoma, depending on the goal of treatment. Definitive RT has the intent of durable irradiated tumor control. Palliative RT has the intent of relieving symptoms caused by tumor.

[zz]See Principles of Imaging–Treatment Response Assessment (ME-D).

[aaa]Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported. Although both trials focused primarily on patients with stage III nodal disease, the NCCN Panel agrees that it is appropriate to extend the indication for adjuvant anti-PD-1 therapy to patients with clinical or macroscopic satellite/intransit disease and who are at significant risk of recurrence.

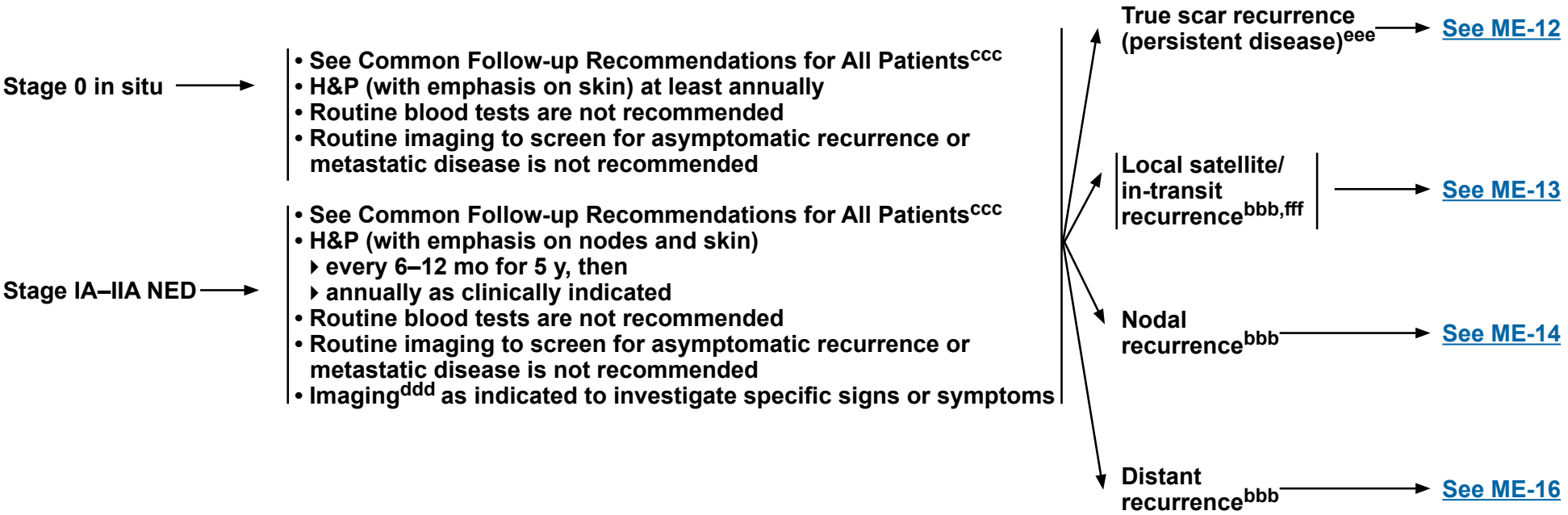
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CLINICAL/ PATHOLOGIC STAGE	WORKUP	
Stage IV Metastatic	• Biopsy to confirm[bbb] • LDH • Imaging[m] for baseline staging and to evaluate specific signs and symptoms	See Treatment for Limited (Resectable) or Disseminated (Unresectable) Disease (ME-16)

[m] See Principles of Imaging–Workup (ME-D).

[bbb] Initial presentation with stage IV disease or clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Biopsy techniques may include core (preferred), FNA, incisional/partial, or excisional. Tissue is always preferred over cytology for mutational analysis. Obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Consider broader genomic profiling if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. See Principles of Biopsy and Pathology (ME-B) and See Principles of Molecular Testing (ME-C).

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



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[ccc] See Common Follow-up Recommendations for All Patients (ME-11).

[ddd] See Principles of Imaging–Follow-up (ME-D).

[eee] True scar recurrence (persistent disease) at the primary tumor wide excision site is defined by the presence of in situ and/or radial growth phase.

[fff] Local satellite/in-transit recurrence without in situ or radial growth phase, with intralymphatic deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar. Satellite and in-transit metastases are biologically and prognostically similar.

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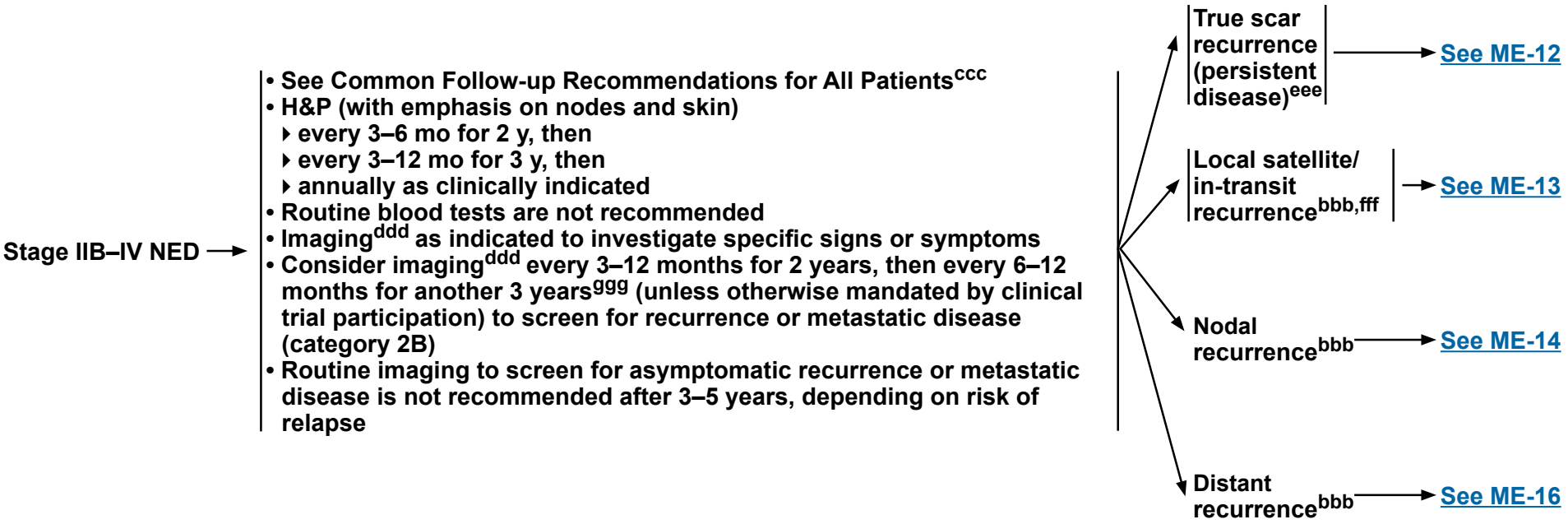

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[ccc] See Common Follow-up Recommendations for All Patients (ME-11).

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[eee] True scar recurrence (persistent disease) at the primary tumor wide excision site is defined by the presence of in situ and/or radial growth phase.

[fff] Local satellite/in-transit recurrence without in situ or radial growth phase, with intralymphatic deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar. Satellite and in-transit metastases are biologically and prognostically similar.

[ggg] The duration and 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 clinical evidence of disease.

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

COMMON FOLLOW-UP RECOMMENDATIONS FOR ALL PATIENTS

- H&P (with emphasis on nodes and skin) at least annually.
- Available, noninvasive pre-biopsy imaging and molecular technologies have not been prospectively compared for diagnostic accuracy. Pre-diagnostic clinical modalities (ie, total-body photography and sequential digital dermoscopy), and other imaging technologies (eg, reflectance confocal microscopy, electrical impedance spectroscopy) may enhance early detection of new primary melanoma in patients with high mole count and/or presence of clinically atypical nevi. Pre-diagnostic noninvasive genomic patch testing be may also be helpful to guide biopsy decisions.
- Patient education in regular skin and lymph node self-examination.
- Patient education in principles of sun safety, including sun avoidance during peak hours, use of sun-protective clothing/hat/eyewear, and regular application of broad-spectrum sunscreen to exposed skin when outdoors, particularly in individuals with sun sensitivity/light complexion.
- In patients with an equivocal lymph node exam, short-term follow-up and/or additional imaging (US [preferred] or CT) should be considered, with imaging-directed biopsy as warranted.
- Regional lymph node US in patients with a positive SLNB who did not undergo CLND should be considered where expertise is available. It would be appropriate for the frequency of clinical exam and US surveillance to be consistent with the two prospective randomized trials (MSLT-II and DeCOG):
  - every 4 months during the first 2 years,
  - then every 6 months during years 3 through 5.
- Follow-up schedule is influenced by risk of recurrence and new primary melanoma, which depends on patient/family history of melanoma, mole count, and/or presence of atypical moles/dysplastic nevi.
- Clinical and family history can identify patients in whom multigene testing might indicate an increased genetic risk for cutaneous and uveal melanoma, astrocytoma, mesothelioma, and cancers of the breast, pancreas, and kidney. This information can guide recommendations for surveillance and early detection in the patient and his/her relatives.
  - Consider genetic counseling referral for p16/*CDKN2A* mutation testing in the presence of 3 or more invasive cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family.
  - Multigene panel testing that includes CDKN2A is also recommended for patients with invasive cutaneous melanoma who have a first-degree relative diagnosed with pancreatic cancer (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic).
  - Testing for other genes that can harbor melanoma-predisposing mutations (See Risk Factors for Melanoma Development ME-A 1 of 2) may be warranted.

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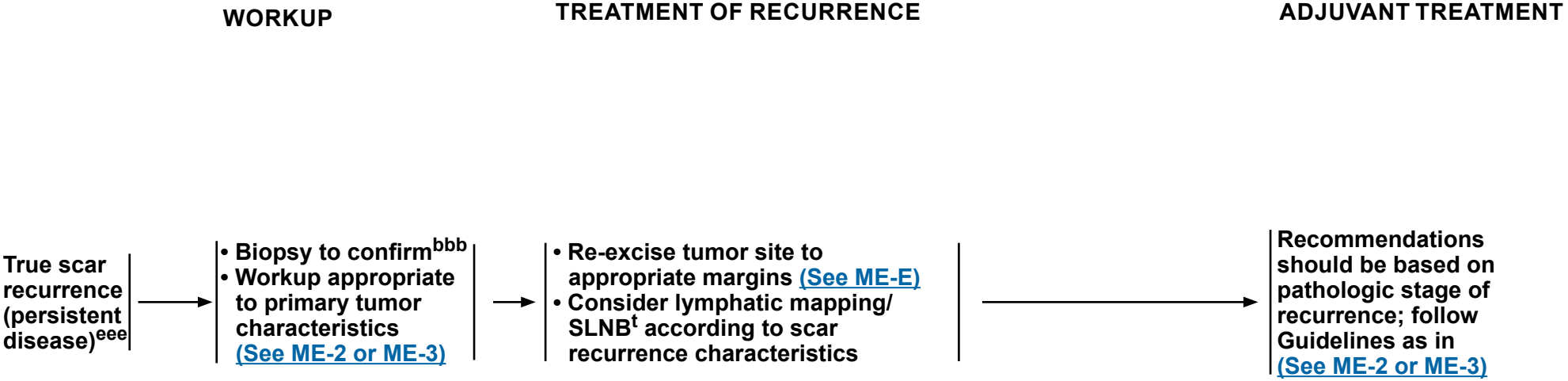

[t] See Principles of Sentinel Lymph Node Biopsy (SLNB) (ME-F).

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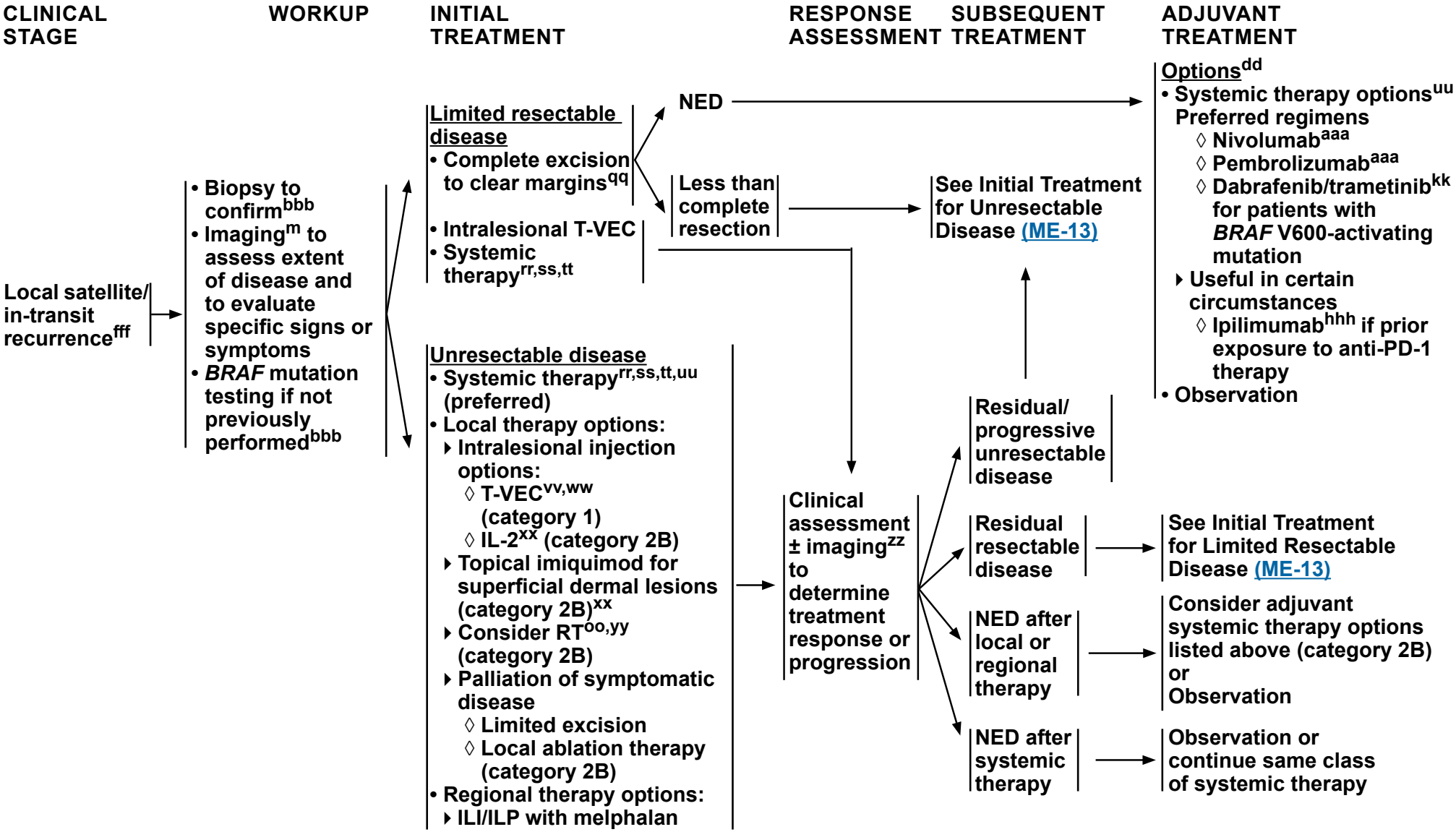

See ME-13A for footnotes

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FOOTNOTES FOR LOCAL SATELLITE/IN-TRANSIT RECURRENCE

[m] See Principles of Imaging–Workup (ME-D).

[dd] The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity. See Systemic Therapy Considerations (ME-J).

[kk] In the event of unacceptable toxicities to dabrafenib/trametinib, other BRAF/MEK inhibitor combinations could be considered.

[oo] See Principles of Radiation Therapy for Melanoma (ME-H).

[qq] Consider sentinel node biopsy for resectable clinical satellite/in-transit disease if it will change treatment options (category 2B). See Principles of Sentinel Lymph Node Biopsy (SLNB) (ME-F).

[rr] See Systemic Therapy for Metastatic or Unresectable Disease (ME-I).

[ss] For low-volume in-transit disease, the high risk of toxicities associated with certain combination regimens may outweigh the benefit.

[tt] Prospective trials supporting the systemic therapy options on ME-I included only a small subset of patients with stage III disease.

[uu] For patients who have previously received systemic therapy for cutaneous melanoma (either as active treatment or adjuvant therapy), selection of systemic therapy regimen should be informed by response to prior systemic therapies. For patients who experienced progression of melanoma during or shortly after a prior therapy, consider agents of a different class. For patients who experience disease control (CR, PR, or SD) on a prior systemic therapy, and have no residual toxicity, but subsequently experienced disease progression/relapse >3 months after treatment discontinuation, systemic therapy with the same agent or same class of agents may be considered.

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[zz] See Principles of Imaging–Treatment Response Assessment (ME-D).

[aaa] Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported. Although both trials focused primarily on patients with stage III nodal disease, the NCCN Panel agrees that it is appropriate to extend the indication for adjuvant anti-PD-1 therapy to patients with clinical or macroscopic satellite/intransit disease and who are at significant risk of recurrence.

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[fff] Local satellite/in-transit recurrence without in situ or radial growth phase, with intralymphatic deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar. Satellite and in-transit metastases are biologically and prognostically similar.

[hhh] In an EORTC prospective randomized trial of adjuvant high-dose ipilimumab at 10 mg/kg (ipi10) versus placebo, ipi10 conferred improved RFS and OS, but was associated with a high incidence of adverse events, including 1% drug-related mortality. However, there were no patients with resected in-transit disease in the adjuvant trial, and therefore the use of adjuvant ipilimumab in this setting is based on extrapolation. In situations where adjuvant ipilimumab may be an option (eg, patients who progress during anti-PD-1 therapy with resectable disease), the recommended dose is 3 mg/kg.

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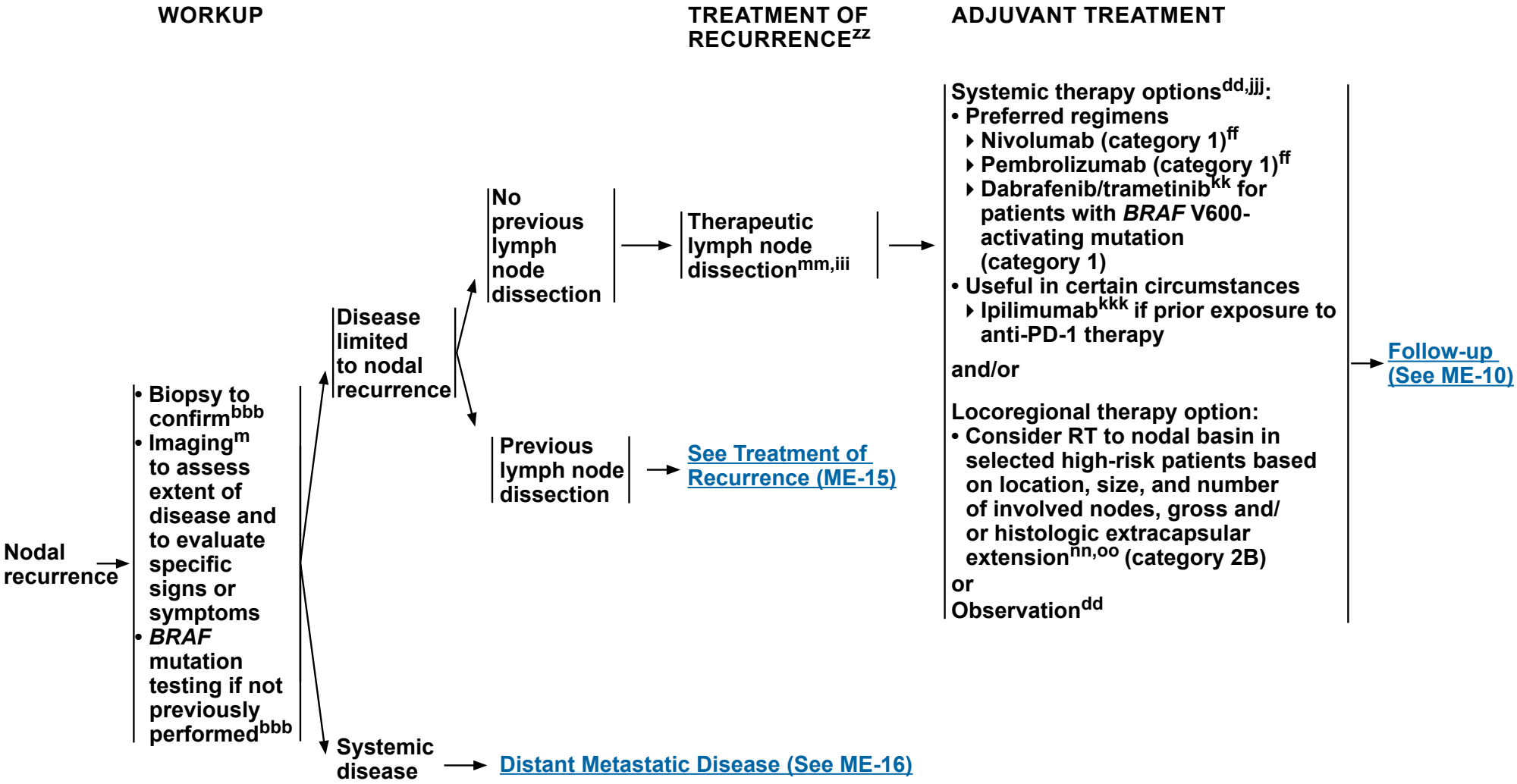

See footnotes on 14A

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FOOTNOTES FOR NODAL RECURRENCE

[m] See Principles of Imaging–Workup (ME-D).

[dd] The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity. See Systemic Therapy Considerations (ME-J).

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[mm] In patients with extensive resectable nodal disease at very high risk of recurrence after complete resection, or if resectability of nodal disease is uncertain, recommend multidisciplinary tumor board review to consider neoadjuvant systemic therapy, preferably in the context of a clinical trial. For patients with unresectable nodal disease, consider treatment with systemic therapy (options shown on ME-I) followed by resection, or treat as stage IV (ME-16). Prospective trials supporting the systemic therapy options on ME-I included only a small subset of patients with stage III disease (unresectable).

[nn] Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in RFS or OS. Its benefits must be weighed against potential toxicities such as lymphedema (limb) or oropharyngeal complications. The impact of these potential toxicities should be considered in the context of available systemic adjuvant treatment options.

[oo] See Principles of Radiation Therapy for Melanoma (ME-H).

[zz] See Principles of Imaging--Treatment Response Assessment (ME-D).

[bbb] Initial presentation with stage IV disease or clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Biopsy techniques may include core (preferred), FNA, incisional/partial, or excisional. Tissue is always preferred over cytology for mutational analysis. Obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Consider broader genomic profiling if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. See Principles of Biopsy and Pathology (ME-B) and See Principles of Molecular Testing (ME-C).

[iii] See Principles of Completion/Therapeutic Lymph Node Dissection (ME-G).

[jjj] For patients who have previously received systemic therapy for cutaneous melanoma (either as active treatment or adjuvant therapy), selection of adjuvant treatment regimen should be informed by response to prior systemic therapies. For patients who experienced progression of melanoma during or shortly after a prior therapy, consider adjuvant agents of a different class. For patients who experience disease control (CR, PR, or SD) on a prior systemic therapy, and have no residual toxicity, but subsequently experienced disease progression/relapse >3 months after treatment discontinuation, adjuvant treatment with the same agent or same class of agents may be considered.

[kkk] In an EORTC prospective randomized trial of adjuvant high-dose ipilimumab at 10 mg/kg (ipi10) versus placebo, ipi10 conferred improved RFS and OS, but was associated with a high incidence of adverse events, including 1% drug-related mortality. In a subsequent Intergroup randomized trial of adjuvant ipilimumab 3 mg/kg (ipi3) versus ipi10 versus high-dose interferon, the incidence of treatment-related adverse events ≥ grade 3 was 37% with ipi3 versus 58% with ipi10. The trial noted a statistically significant OS advantage for ipi3 versus interferon, but a trend for OS advantage of ipi10 over interferon was not statistically significant. In situations where adjuvant ipilimumab may be an option (eg, patients who progress during anti-PD-1 therapy with resectable disease), the recommended dose is 3 mg/kg.

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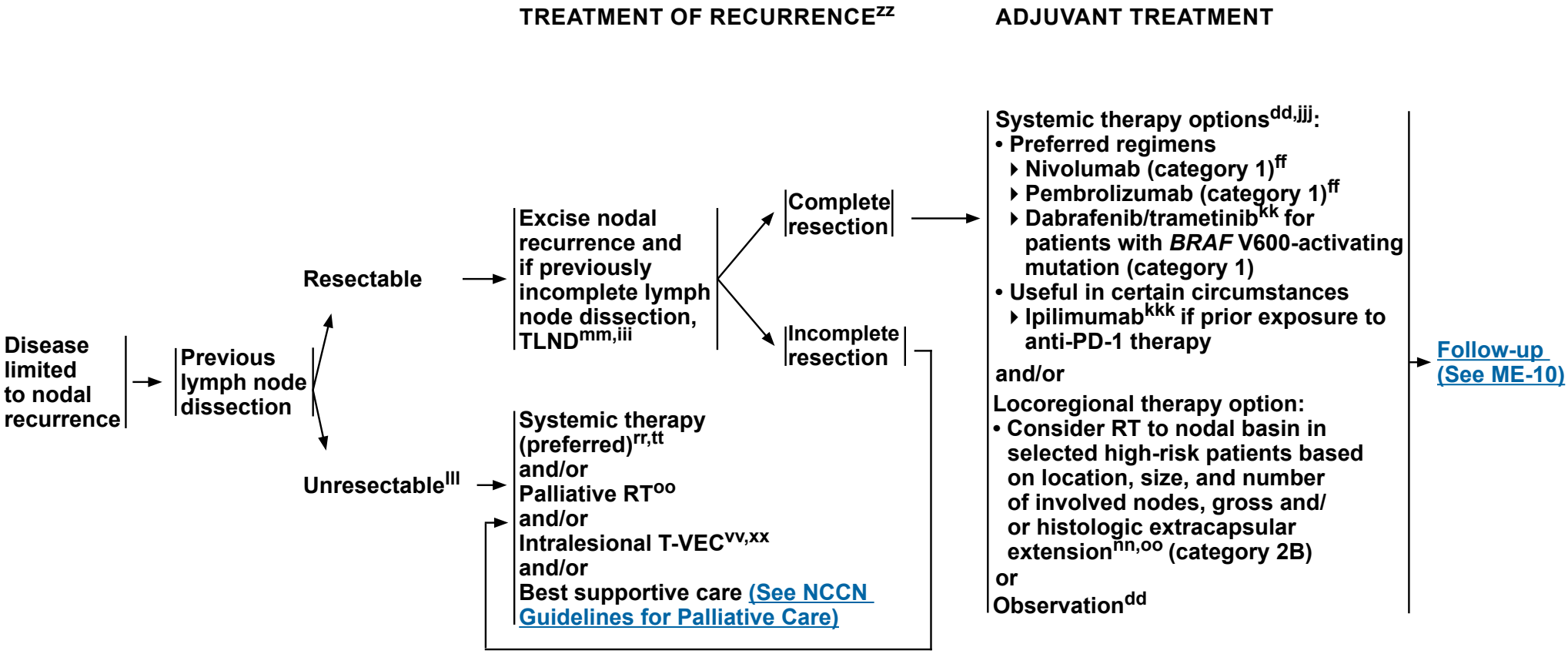

See footnotes on ME-15A

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

FOOTNOTES FOR DISEASE LIMITED TO NODAL RECURRENCE

[dd]The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity. See Systemic Therapy Considerations (ME-J).

[ff]Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported.

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[mm]In patients with extensive resectable nodal disease at very high risk of recurrence after complete resection, or if resectability of nodal disease is uncertain, recommend multidisciplinary tumor board review to consider neoadjuvant systemic therapy, preferably in the context of a clinical trial. For patients with unresectable nodal disease, consider treatment with systemic therapy (options shown on ME-I) followed by resection, or treat as stage IV (ME-16). Prospective trials supporting the systemic therapy options on ME-I included only a small subset of patients with stage III disease.

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[oo]See Principles of Radiation Therapy for Melanoma (ME-H).

[rr]See Systemic Therapy for Metastatic or Unresectable Disease (ME-I).

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[xx]These options have been preference stratified as "Useful In Certain Circumstances."

[zz]See Principles of Imaging--Treatment Response Assessment (ME-D).

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[lll]Disease is defined as technically unresectable (ie, involvement of a major neurovascular structure) or clinically unresectable (ie, remote nodal disease), where surgery alone would have minimal clinical benefit.

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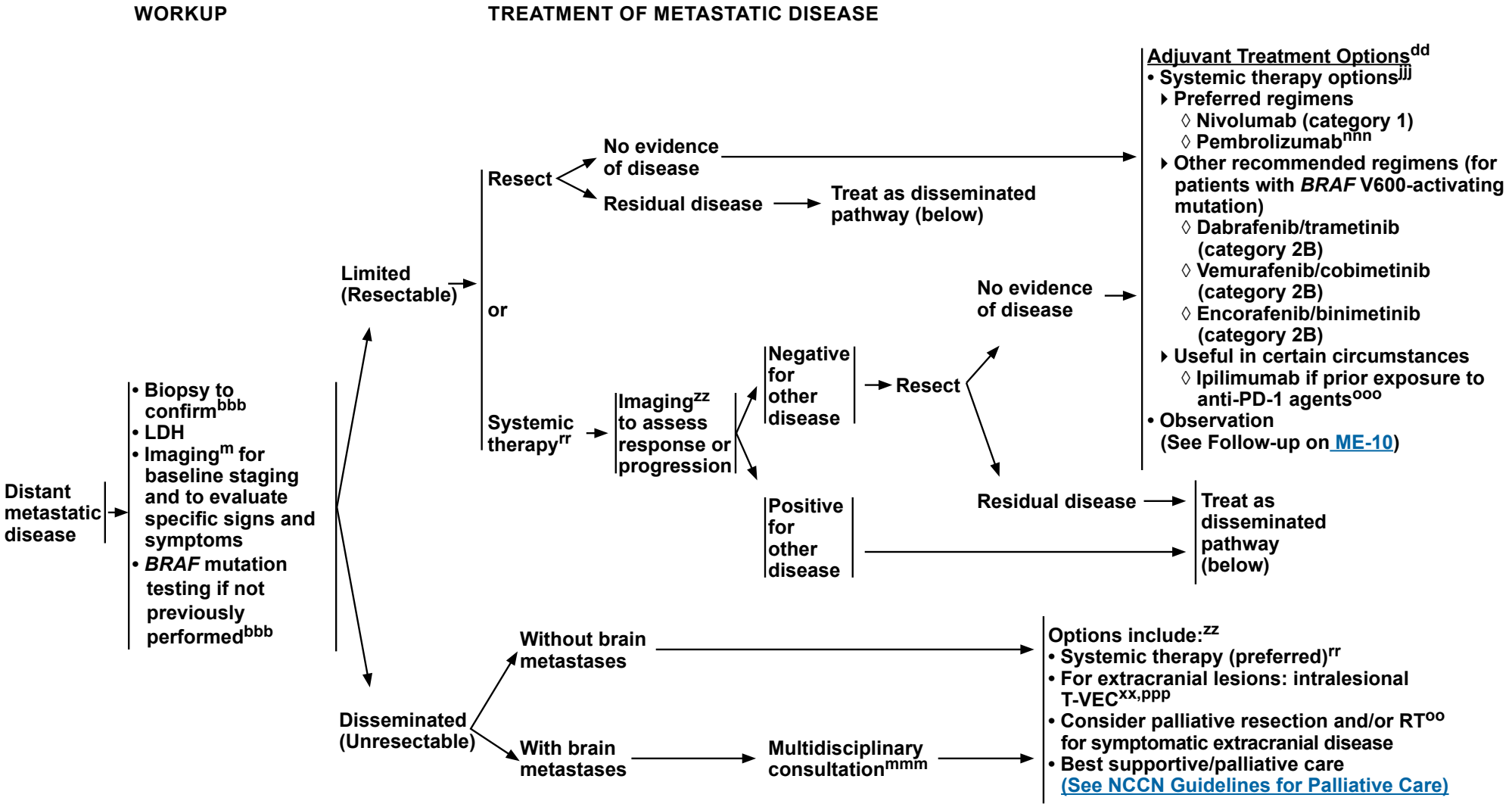

See footnotes on ME-16A

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FOOTNOTES FOR TREATMENT OF METASTATIC DISEASE

[m] See Principles of Imaging–Workup (ME-D).

[dd] The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity. See Systemic Therapy Considerations (ME-J).

[oo] See Principles of Radiation Therapy for Melanoma (ME-H).

[rr] See Systemic Therapy for Metastatic or Unresectable Disease (ME-I).

[xx] These options have been preference stratified as "Useful In Certain Circumstances."

[zz] See Principles of Imaging–Treatment Response Assessment (ME-D).

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[mmm] See Principles of Brain Metastases Management (ME-L).

[nnn] Although patients with resected stage IV disease were not included in the phase III prospective randomized trial testing adjuvant pembrolizumab, it is included as an option here because all available evidence suggests that pembrolizumab and nivolumab have highly similar efficacy and safety in patients with melanoma.

[ooo] Ipilimumab is included as an adjuvant treatment option for patients with resected stage IV disease who have prior exposure to anti-PD-1 agents based on extrapolation of data demonstrating its efficacy as adjuvant treatment for resected stage III disease and demonstrated efficacy for unresectable stage IV disease. In an EORTC prospective randomized trial of adjuvant high-dose ipilimumab at 10 mg/kg (ipi10) versus placebo, ipi10 conferred improved RFS and OS, but was associated with a high incidence of adverse events, including 1% drug-related mortality. In a subsequent Intergroup randomized trial of adjuvant ipilimumab 3 mg/kg (ipi3) versus ipi10 versus high-dose interferon, the incidence of treatment-related adverse events ≥ grade 3 was 37% with ipi3 versus 58% with ipi10. The trial noted a statistically significant OS advantage for ipi3 versus interferon, but a trend for OS advantage of ipi10 over interferon was not statistically significant. In situations where adjuvant ipilimumab may be an option (eg, patients who progress during anti-PD-1 therapy with resectable disease), the recommended dose is 3 mg/kg.

[ppp] T-VEC has shown a response rate (lasting ≥6 months) of 16% in highly selected patients with AJCC 7th Edition stage IV–M1a disease (skin, subcutaneous, and/or remote nodes).

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RISK FACTORS FOR DEVELOPMENT OF SINGLE OR MULTIPLE PRIMARY MELANOMAS[a]

- **Male sex**[1]
- **Age >60 years**
- **Phenotypic predisposition**
  - **Atypical mole/dysplastic nevus pattern**[2]
  - **Increased mole count (particularly large nevi)**[3]
  - **Sun-phenotype/tendency to sunburn**[3]
  - **Red hair-blue eyes/Fitzpatrick skin type I/pheomelanin predominant phenotype**[3]
- **Personal medical history/comorbidities**
  - **Multiple and/or blistering sunburns**[3,4]
  - **Precancer/cancers,**[5,6] **especially:**
    - ◊ **Actinic keratosis/non-melanoma (keratinocyte) skin cancer (eg, basal cell and squamous cell carcinomas)**[3]
    - ◊ **Childhood cancer**[7]
  - **Immunosuppression/immune perturbation related to:**
    - ◊ **Solid organ transplantation**[3,8,9]
    - ◊ **Hematopoietic cell transplantation (HCT)**[9]
    - ◊ **Human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS)**[10]
  - **Rare genodermatoses**
    - ◊ **Xeroderma pigmentosum**[11]
- **Genetic predisposition**
  - **Presence of germline mutations or polymorphisms predisposing to melanoma (eg, *CDKN2a, CDK4, MC1R, BRCA2, BAP1* [especially for uveal melanoma], *TERT, MITF, PTEN*, and potential other genes).**[3,12-14]
  - **Family history of cutaneous melanoma (especially if multiple), pancreatic, renal and/or breast cancer, astrocytoma, uveal melanoma, and/or mesothelioma.**[3,15]
- **Environmental factors**
  - **Tanning bed use**[3,16,17]
  - **Residence in sunnier climate/latitude nearer to equator**[18]
  - **Intermittent, intense sun exposure (for truncal/extremity melanomas, often observed with associated increased nevus count)**[3]
  - **Chronic sun exposure (for head/neck/arm melanomas, often associated with lower nevus count)**

[a]Risk factors for development of single or multiple primary melanomas, including subsequent primaries after index diagnosis. This list does not include risk factors for melanoma recurrence or progression, as those are covered elsewhere in the algorithm.

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RISK FACTORS FOR DEVELOPMENT OF SINGLE OR MULTIPLE PRIMARY MELANOMAS
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PRINCIPLES OF BIOPSY OF A SUSPICIOUS PIGMENTED LESION[1]

- **Excisional/complete biopsy (elliptical, punch, or saucerization/deep shave) with 1- to 3-mm margins preferred. Avoid wider margins to permit accurate subsequent lymphatic mapping.**
- **The orientation of an elliptical/fusiform excisional biopsy should be planned with definitive wide local excision in mind (eg, longitudinally [axially] and parallel to the underlying lymphatics on the extremities).**
- **Full-thickness incisional or punch biopsy of clinically thickest or most atypical portion of lesion is acceptable in certain anatomic areas (eg, palm/sole, digit, face, ear) or for very large lesions. Multiple "scouting" biopsies may help guide management for very large lesions. Superficial shave biopsy may compromise pathologic diagnosis and complete assessment of Breslow thickness, but is acceptable when the index of suspicion is low. However, a broad shave biopsy may be optimal for histologic assessment for melanoma in situ (MIS), lentigo maligna (LM) type (ie, melanoma on skin with high cumulative sun damage [CSD]).**
- **Repeat narrow-margin excisional biopsy is recommended if an initial partial biopsy is inadequate for diagnosis or microstaging but should not be performed if the initial specimen meets criteria for SLN staging.**

Continued

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PRINCIPLES OF PATHOLOGY FOR PRIMARY MELANOMA[a,b,1-5]

- **The biopsy should be reported by a pathologist experienced in melanocytic neoplasms.**
- **Minimal elements to be reported should include factors that inform pathologic T-stage: Breslow thickness (reported to the nearest 0.1 mm), ulceration (present or absent).**
- **Microsatellites should be reported if observed on either initial biopsy or subsequent wide excision.[c,d]**
- **Margin status should be reported on all biopsies and excisions.[e]**
- **Encourage consistent synoptic reporting of additional prognostic criteria, including:[1]**
  - **Presence of macroscopic satellite lesions in the gross tumor specimen.**
  - **Dermal mitotic rate per mm^2 [f]**
  - **Lymphovascular/angiolymphatic invasion[d]**
  - **Histologic subtype (if desmoplastic, specify pure or mixed[g])**
  - **Regression (if extensive [>75%] or extending beneath measured Breslow thickness)**
  - **Neurotropism/perineural invasion**
- **If there is a residual invasive melanoma in the wide excision specimen, the pathologist should incorporate elements of the initial biopsy and wide excision (thickest tumor depth, ulceration) to arrive at a final pathologic T-stage.**
- **Consider the use of molecular testing for histologically equivocal lesions.[h]**

[a]International Collaboration on Cancer Reporting (ICCR, 11/2019) core histopathologic elements for biopsy and wide excision specimens include: macroscopic satellites (in the gross specimen), surgical margin/tissue edges (involved/uninvolved), Breslow thickness, ulceration, mitotic count, microsatellites, lymphovascular invasion, neurotropism, desmoplastic melanoma component ("pure" [>90% desmoplastic] versus "mixed" [desmoplastic/nondesmoplastic]).[2]

[b]College of American Pathologists (CAP, 04/2020) histopathologic elements required for accreditation purposes in the wide excision specimen include: macroscopic satellite nodules, histologic subtype, thickness, ulceration, microsatellites, margins (deep/peripheral - positive or negative for invasive or in situ melanoma), mitotic rate, lymphovascular invasion, neurotropism, regression.[5]

[c]Microsatellitosis represents microscopically identified lymphatic metastasis and confers an increased risk of recurrence. Microsatellites are found discontinuous from the primary tumor (adjacent or deep). The AJCC Cancer Staging Manual, Eighth Edition (2017)[3] does not define microsatellitosis according to tumor nest dimension or distance from the primary tumor. It classifies cases with microsatellites, clinical satellites, or in-transit metastases as N1c, N2c, or N3c based on the number of tumor-involved regional lymph nodes (0, 1, or ≥2, respectively).

[d]At times it may be difficult to distinguish whether invasive melanoma is present within a lymphatic channel or represents a microsatellite. In this instance, the use of immunohistochemistry for a specific lymphatic marker such as D2–40 may assist in distinction.

[e]For histologically positive margins on the biopsy or wide excision specimen, describe whether in situ or invasive melanoma is present at the peripheral and/or deep margins. For histologically negative margins on the wide excision specimen, ICCR and CAP guidelines do not require reporting the microscopically measured distances between tumor and labeled lateral or deep margins, and this measurement should not generally impact clinical decision-making.[2,5]

[f]Dermal mitotic rate should be determined using the "hot spot" technique and expressed as number of mitoses per square millimeter. Although dermal mitotic rate is no longer included in the determination of T1 staging in the AJCC Cancer Staging Manual, Eighth Edition (2017),[3] it remains an important prognostic factor across all thickness categories and should be included in the pathology assessment of melanoma biopsies and surgical excisions.

[g]In patients with pure desmoplastic melanoma (>90% of invasive melanoma associated with prominent stromal fibrosis), SLN positivity is less common compared to mixed desmoplastic/nondesmoplastic and conventional melanoma subtypes. Variability across studies in the rate of SLN positivity in desmoplastic melanoma may be due to lack of standardized criteria for defining pure desmoplastic melanoma, histopathologic reproducibility, and/or reporting. In the setting of these conflicting reports, the role of SLNB in patients with pure desmoplastic melanoma remains controversial.

[h]See Principles of Molecular Testing (ME-C).

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PRINCIPLES OF MOLECULAR TESTING

Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication

- **Diagnostic testing for indeterminate melanocytic neoplasms following histopathology**
  - **Melanocytic neoplasms of uncertain biologic potential present a unique challenge to pathologists and treating clinicians. Ancillary tests to differentiate benign from malignant melanocytic neoplasms include immunohistochemistry (IHC) and molecular testing via comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), single-nucleotide polymorphism (SNP) array, and next-generation sequencing (NGS). These tests may facilitate interpretation of cases that are diagnostically uncertain or controversial by histopathology. Ancillary tests should be used as adjuncts to clinical and expert dermatopathologic examination and therefore be interpreted within the context of these findings.**
- **Prognostic testing**
  - **Commercially available GEP tests are marketed as being able to classify cutaneous melanoma into separate categories based on risk of metastasis.[1-6] However, it remains unclear whether these GEP platforms provide clinically actionable prognostic information when used in addition to or in comparison with known clinicopathologic factors or multivariable nomograms that incorporate patient sex, age, tumor location and thickness, ulceration, mitotic rate, lymphovascular invasion, microsatellites, and SLNB status.[7,8] Furthermore, the impact of these tests on treatment outcomes or follow-up schedules has not been established.**
  - **Various (mostly retrospective) studies of prognostic GEP testing suggest its role as an independent predictor of worse outcome, though not superior to Breslow thickness or SLN status.[3,9,10] It remains unclear whether available GEP platforms are reliably predictive of outcome across the risk spectrum of melanoma.[11-13] Prospective validation studies (as have been performed in breast cancer) are required to more accurately define the clinical utility of molecular testing prior to widespread implementation of GEP for prognostication of cutaneous melanoma, and in particular to determine its role in guiding surveillance imaging, SLNB, and adjuvant treatment decisions.[14] Existing and emerging GEP platforms and other prognostic techniques should also be compared with optimized contemporary multivariable phenotypic models (ie, the AJCC 8th edition melanoma risk calculator/prognostic tool in development).[15-17]**
- **Somatic mutation testing**
  - **A number of somatic genetic alterations have been identified in cutaneous melanoma, a few of which are targetable driver mutations that have proven useful to guide treatment decisions and/or clinical trial eligibility.**

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Continued

PRINCIPLES OF MOLECULAR TESTING

Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication (continued)

- **Specific mutations (*BRAF, NRAS, KIT)* and implications**
  - ***BRAF*** **(B-Raf proto-oncogene) mutations:**
    - **BRAF is a serine threonine kinase that activates the mitogen-activated kinase pathway. Mutations in this gene lead to unrestrained cell growth and proliferation.**
    - **Some clinical features are associated with a higher frequency of *BRAF* mutations (eg, intermittent sun-exposed skin, younger age, trunk location), but these should not be used either as a proxy for these mutations or to decide testing.[18]**
    - ***BRAF*** **mutations are most commonly found in the 600th codon (V600), most frequently V600E (80%) but also including V600K (15%) and V600R/M/D/G (5%).[19]**
      - ***BRAF*** **V600 mutations are associated with sensitivity to BRAF inhibitors. Available evidence suggests that BRAF inhibitors should not be used in patients without *BRAF* V600 mutations.[20]**
      - ***BRAF*** **V600 mutations are also associated with sensitivity to MEK inhibitors.[21]**
      - **Clinical trials have shown that the combination of BRAF and MEK inhibitors are superior to either agent alone in patients with *BRAF* V600 mutations.[22]**
      - **Extensive clinical trial data have shown that compared with *BRAF* V600E, patients with *BRAF* V600K-mutated metastatic melanoma may have slightly lower response/benefit when treated with BRAF ± MEK inhibitors. Less frequent mutations affecting codon 600 (including V600R/M/D/G) also may benefit from these therapies.[23,24]**
    - ***BRAF*** **mutations outside of the 600th codon (*BRAF* non-V600 mutations) and *BRAF* fusions are also found in approximately 5% of melanomas.**
      - **Mutations in codons near V600 in exon 15 (specifically *BRAF* L597 and *BRAF* K601) have shown response to MEK inhibitors and BRAF and MEK inhibitor combinations.[25,26]**
      - **Fusions in *BRAF* have also shown responses to MEK inhibitors and non-specific RAF inhibitors (eg, sorafenib).[27,28]**
      - **Mutations in other codons in exon 11 or exon 15 have not demonstrated response to either BRAF or MEK inhibitors.**
  - ***KIT*** **(proto-oncogene c-KIT) mutations**
    - ***KIT*** **is a receptor tyrosine kinase that promotes cell growth and proliferation.**
    - ***KIT*** **mutations are present in 10%–15% of melanomas of mucosal (most frequently vulvovaginal primaries, but also anorectal and sinonasal) and acral (ie, non–hair-bearing surfaces of palms and soles, nailbeds) origin. They are also present on 2%–3% of chronically sun-exposed skin, but extremely rarely on skin with intermittent sun exposure. Thus, clinical features can guide the decision whether to perform *KIT* mutation testing.[29]**
    - **KIT mutations may occur in multiple "hotspots" across the gene and differ in their sensitivity to KIT inhibitors (eg, imatinib, sunitinib, nilotinib).[30-32]**
      - ***KIT*** **exon 11 and exon 13 mutations (eg, W557, V559, L576P, K642E) appear to have a high level of sensitivity to KIT inhibition.**
      - ***KIT*** **exon 17 mutations (eg, D816H) appear to have minimal or no sensitivity to KIT inhibitors.**
      - ***KIT*** **amplifications appear to have minimal or no sensitivity to KIT inhibitors.**

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Continued

PRINCIPLES OF MOLECULAR TESTING

Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication (continued)

- **Specific mutations (*BRAF, NRAS, KIT*) and implications (continued)**
  - ***NRAS* (NRAS proto-oncogene) mutations**
    - **NRAS is a GTPase that activates mitogen-activated protein kinase signaling and other signaling pathways, leading to cell growth and proliferation.[33]**
    - ***NRAS* mutations appear to correlate with poor survival in localized and advanced melanoma.[34]**
    - ***NRAS* mutations are present in approximately 15% of melanomas in skin with chronic and intermittent sun exposure, acral surfaces, and mucosal surfaces.[18]**
    - **MEK inhibitors may produce responses in a minority of patients with *NRAS* mutations[35]**
    - **Given the low probability of overlapping targetable mutations (including *BRAF* and *KIT* mutations), the presence of an *NRAS* mutation may identify patients who will not benefit from additional molecular testing.**

- **Other uncommon mutations detected by NGS panel**
  - **Fusions in *NTRK1*, *NTRK2*, and *NTRK3* occur uncommonly (<1%) across subtypes of melanoma.[36]**
    - **Fusions in these genes correspond with a high response rate to the TRK inhibitors larotrectinib or entrectinib.[37,38]**
  - **Fusions in *ALK* and *ROS1*, more common in lung cancer, occur uncommonly (<1% incidence) across subtypes of melanoma.[39]**
    - **Fusions in these genes may predispose to clinical activity from inhibitors of these genes (eg, crizotinib, entrectinib).[38]**

- **Methods of mutation testing**
  - **IHC is a technique to selectively visualize antigens (proteins) in tissue section by using antibodies that bind to those specific antigens. IHC may be used to screen for both *BRAF* V600E and c-KIT. This is an indirect test that detects the mutated protein.**
    - **BRAF VE1 (V600E) IHC test may be used as a rapid screening test for assessment of *BRAF* status in melanoma and for potential start of BRAF inhibitor treatment regimen. The sensitivity and the specificity of the VE1 antibody is reported at 89.2% and 96.2%, respectively, with the positive and negative predictive values at 97.1% and 86.2%, respectively. Confirmatory *BRAF* molecular testing is encouraged.[40,41]**
    - ***KIT* IHC testing may be used as a screening tool for assessment of *KIT* status in acral lentiginous or mucosal melanoma. Due to the wide range of different *KIT* mutations and lack of widespread use of this test, confirmatory *c-KIT* molecular testing is encouraged to avoid false positives or negatives.[42]**
  - **NGS, also known as high-throughput sequencing, describes a number of different sequencing technologies that allow sequencing of DNA and RNA much more quickly and cheaply than the previously used Sanger sequencing. Single-gene or small multigene panels are also used in some cases to test either one gene (*BRAF*) or a limited number of genes.**

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Continued

PRINCIPLES OF MOLECULAR TESTING

Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication (continued)

- **Indications for genetic testing**
  - **The panel does not recommend *BRAF* or NGS testing for resected stage I–II cutaneous melanoma unless it will inform clinical trial participation.**
  - ***BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom future *BRAF*-directed therapy may be an option.**
  - **For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (eg, larger NGS panels, *BRAF* non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial.**
  - **If *BRAF* single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (eg, KIT, *BRAF* non-V600).**

- **Biomarkers with potential utility for immune therapy**
  - **PD-L1 (Programmed Death-Ligand 1)**
    - **PD-L1 is a co-regulatory molecule that can be expressed by tumor cells and tumor-infiltrating macrophages, and inhibit T-cell–mediated anti-tumor responses. PD-1, a receptor on T cells, binds to PD-L1, thus inhibiting T-cell activation.[43]**
    - **IHC for PD-L1 may help identify patients more likely to respond to immune checkpoint inhibitors.**
      - **Various antibody clones have been developed for IHC analysis of PD-L1 expression, and while several have shown relative equivalence, others have not.**
      - **Interpretation of PD-L1 IHC is typically focused on the proportion of tumor cells expressing membranous staining at any level and therefore is a continuous variable.**
      - **The threshold to define a clinically relevant elevated level of PD-L1 expression is dependent on the antibody and platform deployed, which may be unique to each checkpoint inhibitor therapy. The multiple different assays for PD-L1 has raised concern among both pathologists and oncologists.[44]**
      - **High PD-L1 expression (>5%) may be a marker for equivalent outcomes with nivolumab monotherapy versus combination ipilimumab and nivolumab in patients with unresectable or metastatic melanoma. Low PD-L1 expression may be a marker for worse outcome with nivolumab monotherapy compared to ipilimumab/nivolumab combination. Even in these scenarios (ie, very high or very low PD-L1 expression), the routine use of PD-L1 expression for treatment decisions is not recommended.[45]**
      - **Testing for tumor PD-L1 should not guide clinical decision-making. The utility of this biomarker requires further investigation.[45]**

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Continued

PRINCIPLES OF MOLECULAR TESTING

Emerging Molecular Technologies for Cutaneous Melanoma Diagnosis and Prognostication (continued)

- **Biomarkers with potential utility for immune therapy (continued)**
  - **Somatic mutation burden**
    - **The total number of mutations present in a tumor (mutation burden) appears to correlate with response to immune checkpoint inhibitors (both with combination ipilimumab and nivolumab, and single-agent anti-PD-1 agents) in melanoma and other cancers.[46,47]**
    - **The mechanism of this effect may relate to increasing numbers of mutations producing increasing neoantigens, proteins that appear foreign to the immune system.[48]**
    - **While whole-exome sequencing is the only way to definitively quantify mutation burden, studies have shown that mutation burden assessed by targeted NGS strongly correlates with results from whole-exome sequencing assays, and shows similar correlation with immune checkpoint inhibitor responses.[49-51]**
    - **The use of mutation burden to guide treatment decisions remains investigational at this time.**

- **Reasons for retesting metastatic tissue**
  - ***BRAF* and *KIT* mutations appear to be early genetic driver events in melanoma.[52] Thus, repeat molecular testing upon recurrence or metastases is likely to be of low yield.**
  - **Repeat testing following progression on targeted therapy (*BRAF*- or *KIT*-directed therapy) does not appear to have clinical utility, since the mechanisms of resistance are diverse and do not have prognostic or therapeutic relevance.[53]**
  - **While the V600E mutation is the most common *BRAF* mutation, other *BRAF* mutations exist that may respond equally well to BRAF inhibitors. Some tests have lower sensitivity/specificity or detect only particular mutations. If needed for clinical care, repeat testing using a different methodology may be warranted to detect non-V600E *BRAF* mutations, or other mutations in different genes. If the initially submitted tissue was of poor quality, a new biopsy may be required before repeat testing is ordered.**

- **Molecular testing requirements**
  - **Use of a properly accredited laboratory (CLIA or CAP)**
  - **Understanding which types of samples (fresh, fresh frozen, formalin-fixed paraffin-embedded) are needed for different test methodologies and are accepted by the testing laboratory**
  - **Understanding the methodologies used and their limitations**
  - **Understanding for each specific method the spectrum of alterations that can and cannot be tested**
  - **Understanding whether the tumor sample was histologically reviewed and representatively sampled**

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Continued

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

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PRINCIPLES OF MOLECULAR TESTING
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PRINCIPLES OF IMAGING[1-10]

Imaging modalities include:

- **Nodal basin US for regional lymph node assessment.**
- **Cross-sectional imaging studies include chest/abdominal/pelvic (and neck if clinically indicated) CT with intravenous (IV) contrast and/or whole-body FDG PET/CT.[a]**
- **Brain MRI with IV contrast**
- **There is non-uniform application of chest x-ray in surveillance and monitoring of patients with advanced melanoma across NCCN Member Institutions.**
- **Scans should be performed with IV contrast unless contraindicated. IV contrast not necessary for CT chest screening for lung metastases.**

[a]Choice of modality depends on clinical circumstances. Multiple retrospective studies suggest that FDG PET/CT may be more sensitive in diagnosing distant metastases, especially in the extremities.[11-16]

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Continued
References

PRINCIPLES OF IMAGING[1-10]

Workup (Baseline)

- **Imaging to evaluate specific signs or symptoms suggestive of possible metastases is recommended in all stages.**
- **Stage-specific recommendations for routine imaging during workup are summarized below.**

- **Stage 0, IA, IB, II**
  - **Routine cross sectional with or without brain imaging is not recommended.**
  - **Stage I/II: Consider nodal basin US prior to SLNB for melanoma patients with an equivocal regional lymph node physical exam. Abnormalities or suspicious lesions on nodal basin US should be confirmed histologically. Nodal basin US is not a substitute for SLNB. Negative nodal basin US is not a substitute for biopsy of clinically suspicious lymph nodes.**

- **Stage IIIA (sentinel node positive)**
  - **Consider cross-sectional imaging for baseline staging.**

- **Stage IIIB/C/D**
  - **Cross sectional with or without brain imaging for baseline staging**

- **True scar recurrence (persistent disease)[b]**
  - **Imaging workup should be appropriate to primary tumor characteristics (see above recommendations for stage 0, IA, IB, II).**

- **Stage IV or recurrence with distant metastatic disease**
  - **Cross sectional and brain imaging**

- **Local satellite/in-transit recurrence;[c] nodal recurrence**
  - **Cross sectional with or without brain imaging to assess extent of disease**

[b]True scar recurrence (persistent disease) is defined by the presence of in situ and/or radial growth phase.
[c]Local satellite/in-transit recurrence without in situ or radial growth phase, with intralymphatic deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar. Satellite and in-transit metastases are biologically and prognostically similar.

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Continued
References

PRINCIPLES OF IMAGING[1-10]

Treatment Response Assessment

- **For patients rendered NED by surgery, imaging recommendations are in the *Follow-up* section.**
- **For active treatment other than complete surgical resection, assessment of response is appropriate, and should include clinical examination and/or imaging (cross sectional ± brain). For patients receiving active non-surgical treatment, imaging throughout treatment at clinically appropriate intervals is recommended in the following clinical settings:**
  - **Stage III (clinical satellite or in-transit[d]) primary or local, satellite, and/or in-transit recurrence[c]**
  - **Nodal recurrence in previously dissected nodal bed that is unresectable[e] or incompletely resected**
  - **Limited (resectable) distant metastatic disease**
  - **Disseminated (unresectable) distant metastatic disease**

[c]Local satellite/in-transit recurrence without in situ or radial growth phase, with intralymphatic deep dermal or subcutaneous fat recurrence within the melanoma scar or satellite metastasis adjacent to the melanoma scar. Satellite and in-transit metastases are biologically and prognostically similar.

[d]Intralymphatic metastases can be characterized as clinically or pathologically detectable satellite metastases (visible or microscopic cutaneous and/or subcutaneous metastases occurring within 2 cm of the primary melanoma), or in-transit metastases (regional cutaneous and/or subcutaneous metastases identified at a distance >2 cm from the primary melanoma). The 2-cm cutoff is consistent with AJCC staging definitions. Satellite and in-transit metastases are biologically and prognostically similar.

[e]Disease can be technically unresectable (eg, involvement of a major neurovascular structure), or clinically unresectable (eg, remote nodal disease), where surgery alone would have minimal clinical benefit.

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Continued
References

PRINCIPLES OF IMAGING[1-10]

Follow-up (surveillance for recurrence in patients with no evidence of disease)

- **Surveillance duration and interval should be tailored to stage and based on assessment of risk factors for recurrence. The intensity and interpretation of cross-sectional imaging should also be influenced by the potential for false positives, the desire to avoid unnecessary invasive tests or 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.**
  - **In patients with an equivocal lymph node exam, short-term follow-up and/or additional imaging (US [preferred] or CT) should be considered, with imaging-directed biopsy as warranted.**
  - **Regional lymph node US in patients with a positive SLNB who did not undergo CLND should be considered where expertise is available. It would be appropriate for the frequency of clinical exam and US surveillance to be consistent with the two prospective randomized trials (MSLT-II and DeCOG): every 4 months during the first 2 years, then every 6 months during years 3 through 5.**
  - **Where radiologic expertise is available, regional nodal US may be utilized in higher risk (eg, T3/T4) melanomas if SLNB is not performed or not technically feasible. Nodal basin US is not a substitute for SLNB.**
- **Stage 0 in situ**
  - **Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended.**
- **Stage IA–IIA (NED)**
  - **Imaging (cross sectional) as indicated to evaluate specific signs or symptoms.**
  - **Routine imaging (cross sectional) to screen for asymptomatic recurrence or metastatic disease is not recommended.**
- **Stage IIB–IV (NED)**
  - **Imaging (cross sectional ± brain) as indicated to evaluate specific signs or symptoms.**
  - **Consider imaging (cross sectional ± brain) every 3−12 months for 2 years, then every 6–12 months for another 3 years (unless otherwise mandated by clinical trial participation) to screen for recurrence or metastatic disease (category 2B).**
    - **◊ More frequent surveillance with brain MRI is recommended for patients with prior brain metastases.**
    - **◊ Periodic brain MRI for up to 3 years may be appropriate to screen for asymptomatic brain metastases in high-risk patients who had stage IIIC or higher without prior central nervous systemic (CNS) metastases.**
    - **◊ There is non-uniform application of chest x-ray in surveillance and monitoring of patients with advanced melanoma across NCCN Member Institutions.**
  - **Routine imaging to screen for asymptomatic recurrence or metastatic disease is not recommended after 3–5 years, depending on risk of relapse.**

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PRINCIPLES OF IMAGING
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PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

Tumor Thickness	Recommended Clinical Margins[b,1-10]
In situ[a]	0.5–1.0 cm
≤1.0 mm	1.0 cm (category 1)
>1.0–2 mm	1–2 cm (category 1)
>2.0–4 mm	2.0 cm (category 1)
>4 mm	2.0 cm (category 1)

- **Wide local excision involves removal of all tissue to the level of the fascia, which is typically preserved unless involved by tumor. Peripheral resection margins may be modified to accommodate individual anatomic or functional considerations. However, the safety and efficacy of narrower surgical margins have not been prospectively studied in a randomized controlled manner. Narrower than recommended margins may increase the risk for margin positivity and/or local recurrence.**
- **The gold standard for histologic assessment of excised melanoma is use of permanent sections. Consider delay of complex reconstruction or wound closure until histologic margin assessment is complete.**
- **Mohs micrographic surgery (MMS) is not recommended for primary treatment of invasive cutaneous melanoma. It may be considered selectively for minimally invasive melanomas when standard margins cannot be achieved in anatomically constrained areas, along with other surgical methods that provide comprehensive histologic assessment, such as staged excision with permanent sections for dermatopathology review.[a]**
- **With respect to disease-related outcomes, there have been no prospective comparisons of different excision methods, including conventional wide excision, MMS, and staged excision with permanent sections. All randomized controlled trials of resection margins for invasive cutaneous melanoma were performed using standard wide excision technique.[1-10] Of note, few included head/neck melanomas and none included acral melanomas.**

[a]For large and/or poorly defined MIS, lentigo maligna (LM) or acral lentiginous subtypes, or LM melanoma with a minimally invasive (T1a) component (also referred to as high-cumulative sun damage [CSD] melanoma), surgical margins >0.5 cm may be necessary, and techniques for comprehensive histologic assessment of margins (ie, complete circumferential peripheral and deep margin assessment) should be considered.[11-16] If MMS is performed, permanent section analysis of the central debulking specimen is recommended to provide complete staging information. For selected patients with positive margins after surgery, in whom further resection is not feasible or desirable, consider topical imiquimod (for patients with MIS/LM type) or RT.

[b]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). However, narrower peripheral histologic margins have been associated with higher rates of local recurrence for invasive melanoma, though not worse melanoma-specific survival.[17-20] Narrow pathologic margins, particularly of the invasive component, may warrant further surgical resection.

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PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA
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PRINCIPLES OF SENTINEL LYMPH NODE BIOPSY (SLNB)

General Principles

- **SLNB is a surgical procedure developed to accurately stage patients with cutaneous melanoma through pathologic assessment of the regional nodal basin(s) and to provide prognostic information for patients with clinical stage I/II melanoma (no clinical or radiographic evidence of nodal disease).**
- **In patients with clinical stage I/II melanoma, SLN status is the strongest predictor of survival. The peformance of SLNB does not impact survival.**
- **SLN status may impact future therapeutic decisions, including recommendations for active nodal basin US surveillance or CLND, adjuvant therapy, and type/frequency of clinic visits and/or surveillance imaging.**
- **Certain pathologic features of the primary tumor are associated with higher risk of SLN positivity, with tumor thickness being the most reliable predictor of a positive SLNB.**
- **NCCN makes recommendations on when to perform SLNB based on the likelihood that a patient will have a positive SLNB.**
- **SLNB should be discussed with all patients with clinical stage IB or II melanoma, with the following considerations:**
  - **For patients with a melanoma Breslow depth of <0.8 mm without ulceration (T1a), the probabilty of a positive SLN is less than 5%. NCCN does not generally recommend SLNB for these patients unless there is significant uncertainty about the adequacy of microstaging (eg, positive deep margins).**
  - **For patients with clinical stage IB, T1b melanoma (Breslow depth <0.8 mm with ulceration or 0.8–1 mm with or without ulceration), or T1a lesions with Breslow depth <0.8 mm and with other adverse features (eg, mitotic index >2/mm^2 [particularly in the setting of young age], lymphovascular invasion, or a combination of these factors), the probability of a positive SLNB is 5%–10%. NCCN recommends discussing and considering SLNB for these patients.**
  - **For patients with stage IB (T2a) or II (T2b and higher) melanoma, the probability of a positive SLN is generally greater than 10%. However, there are subsets of patients (non-mitogenic, or older patients) for whom the probability of a positive SLN is substantially lower.[1,2] NCCN recommends discussing and offering SLNB for these patients.**
  - **Regardless of a patient's risk of a positive SLNB, if he/she is medically unfit or is unlikely to act on the information that the SLNB would provide (eg, pursue surveillance nodal basin US, undergo CLND, consider adjuvant therapy, or change follow-up schedules), then it is reasonable to forego SLNB.**
  - **Prognostic GEP testing to differentiate melanomas at low versus high risk for metastasis should not replace pathologic staging procedures. Currently available GEP tests should not be used to determine SLNB eligibility.**
- **Although the accuracy of SLNB may be lower after a prior wide excision, rotational flap, or skin graft closure of a primary melanoma, it may be considered in this setting.**
- **In the setting of an isolated in-transit metastasis or local recurrence of a primary melanoma without clinically or radiographically evident regional nodal or distant metastases, SLNB may be considered.**

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PRINCIPLES OF SENTINEL LYMPH NODE BIOPSY (SLNB)

Principles of Nuclear Medicine

- Patients undergo preoperative lymphoscintigraphy to identify the regional lymph basin and the individual SLNs within that basin.
- Generally, 0.5–1.0 mCi of Tc-99m radiocolloid is injected intradermally in 4 to 5 locations around the biopsy site. Dynamic and static images may be obtained.
- In selected cases, especially the head and neck and pelvic regions, SPECT-CT imaging may be performed as an adjunct to planar imaging to better define the anatomic location of the sentinel node(s).
- Lymphoscintigraphy may be carried out the day of surgery or the day prior. If performed the afternoon prior, a higher dose of radiocolloid should be used and the case should be performed as early as possible the following day.
- Imaging should include all potentially relevant anatomic nodal basins as well as sites outside of recognized node basins. This would include the entire limb for extremity melanomas; and bilateral inguinal, axillary, and cervical nodal basin imaging for truncal melanomas; and pelvic nodal basin imaging for lower extremity and low truncal melanomas.

Principles of Surgery

- Lymphatic mapping is generally performed prior to wide local excision if performed at the same procedure. If the primary site is close to the SLNB nodal basin and interferes with gamma probe use/counts, it is acceptable to perform the primary tumor wide excision prior to SLNB.
- When used, blue dye (commonly isosulfan blue or methylene blue) is injected intradermally (not subcutaneously) with a fine-gauge needle at the site of the primary lesion. Massage of the primary lesion is not usually necessary.
- An incision is made in the regional lymph basin of the expected lymphatic drainage, over the site of the highest transcutaneous gamma counts, orienting the wound to be compatible with possible future CLND. Once the skin incision over the SLN has been made, limited gamma probe-directed exploration of the tissue is performed to identify SLN(s).
- Once identified and removed, the SLN is examined with the gamma probe ex vivo. Further nodal exploration and SLN are identified if their maximum gamma counts are >10% of the highest SLN count and/or are blue in color.
- In the case of a lower-extremity melanoma with iliac nodes on the same lymphatic channel as a more proximal superficial femoral SLN, excision of the second order nodes may be omitted. However, if they are on a distinct lymphatic channel or there is uncertainty as to their drainage pattern, these SLNs should be identified and excised.
- In-transit (interval or ectopic) SLNs identified that are more proximal than the draining nodal basin should also be excised.

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

PRINCIPLES OF SENTINEL LYMPH NODE BIOPSY (SLNB)

Principles of Pathology

- **SLN(s) should not be sent for frozen section analysis.**
- **SLN(s) are fixed in formaldehyde and embedded in paraffin for subsequent analysis.**
- **For histologic examination, whether for sentinel node analysis or for routine regional lymph node evaluation, the entire node should be submitted. For routine evaluation, large lymph nodes may be bisected or sliced at 2-mm intervals, whereas smaller nodes (<5 mm) may be submitted whole. SLN(s) should be analyzed via standard hematoxylin and eosin (H&E) and immunohistochemistry stains such as HMB45, S100, MELAN-A, or SOX-10.[3]**
- **In cases where the histologic findings in the SLN are equivocal, comparison of cytomorphology to that of the primary tumor, additional immunohistochemistry staining for PRAME (for differentiation of nodal nevi vs. melanoma metastasis), and/or consultation with an experienced dermatopathologist should be considered.[4-6]**
- **Caution should be used when calling an SLN positive based solely upon immunohistochemistry staining of rare, small cells that lack cytomorphologic atypia. Positive staining of rare non-melanoma cells may be seen in lymph nodes with a variety of immunohistochemistry stains used to detect melanocytes. Correlation of the immunohistochemistry stain with the H&E slide is recommended. Additional H&E levels and immunohistochemistry stains may be useful.[3,7-8]**
- **The number of positive and negative SLNs examined should be recorded. If metastases are present, the greatest dimension of tumor size (in mm, measured to the nearest 0.1 mm using an ocular micrometer), location within the lymph node, and presence of extracapsular extension should be recorded.**

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PRINCIPLES OF COMPLETION/THERAPEUTIC LYMPH NODE DISSECTION

Adequacy of Regional Lymph Node Dissection

- **An anatomically complete dissection[a] 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).**
- **For a positive Cloquet's node (as part of a superficial inguinal lymph node dissection), iliac and obturator lymph node dissection may be considered, but is not mandatory given the effectiveness of modern adjuvant therapy.**
- **Therapeutic iliac and obturator lymph node dissection may be considered if imaging shows resectable lymphadenopathy.[b]**
- **For primary melanomas of the head and neck with clinically or microscopically positive lymph nodes in the parotid gland, a superficial parotidectomy with facial nerve preservation[c] and appropriate neck dissection of the draining nodal basins is recommended.**

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

[b]In patients with extensive resectable nodal disease at very high risk of recurrence after complete resection, or if resectability of nodal disease is uncertain, recommend multidisciplinary tumor board review to consider neoadjuvant systemic therapy, preferably in the context of a clinical trial. For patients with unresectable nodal disease, consider treatment with systemic therapy (options shown on ME-I) followed by resection, or treat as stage IV (ME-16).

[c]There is published retrospective single-center experience showing that total parotidectomy may be associated with a lower nodal recurrence rate, but there is a potential for significant morbidity. If used, total parotidectomy should be performed by specialists with training and experience in performing this procedure, to minimize damage to the facial nerve.

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PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

General Treatment Information: Consider RT in the following situations:

- **Modalities: Adjuvant nodal external beam RT (EBRT) should be delivered using a technique judged optimal by the treating radiation oncologist. Newer technologies, such as intensity-modulated RT (IMRT) may lower toxicity and should be considered when available and where appropriate.[1,2] Image-guided RT (IGRT) should be used to improve accuracy of radiotherapy delivery, where clinically appropriate.**

Primary Disease:

- **Definitive Therapy**
  - **Definitive radiation may be considered as a treatment option for MIS, LM-type (ie, high-CSD) in medically inoperable patients or those in whom surgical morbidity of complete resection would be prohibitive.[3-5]**
  - **Dosing Regimens: Optimal doses are not well established, but potential regimens include:[a]**
    - ◊ **64–70 Gy in 32–35 fractions over 6–7 weeks**
    - ◊ **50–57.5 Gy in 20–23 fractions over 4–5 weeks[4,6]**
    - ◊ **35 Gy in 5 fractions over 1 week for fields <3 cm^2[2]**
    - ◊ **32 Gy in 4 fractions once per week[7]**
  - **There are insufficient data to support the routine use of electronic surface brachytherapy in the management of cutaneous melanoma.**

- **Adjuvant Therapy**
  - **Adjuvant radiation may be considered for select cases of high-risk desmoplastic melanoma based on a combination of risk factors for local recurrence.[b,8] (category 2B)**
  - **Dosing Regimens: Optimal adjuvant doses are not well established, but potential regimens include:[a]**
    - ◊ **60–66 Gy in 30–33 fractions over 6–7 weeks[9,10]**
    - ◊ **48 Gy in 20 fractions over 4 weeks[11]**
    - ◊ **30 Gy in 5 fractions over 2 weeks (twice per week or every other day)[12]**

[a]Hypofractionated regimens may increase the risk for long-term complications.
[b]Risk factors for local recurrence include location on the head or neck, extensive neurotropism, pure desmoplastic melanoma histologic subtype, close margins where re-resection is not feasible, or locally recurrent disease.

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Continued
References

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Regional Disease

- **Adjuvant Therapy for High-Risk Resected Regional Disease**
  - **Adjuvant nodal basin RT is associated with reduced lymph node field recurrence in patients at high risk for regional recurrence, but is not associated with improved relapse-free survival (RFS) or overall survival (OS).[7,13,14] The benefit of RT must be weighed against potential toxicities, such as lymphedema (limb) or oropharyngeal complications. The impact of these potential toxicities should be considered in the context of newer adjuvant systemic options.**
  - **Risk factors for regional recurrence include gross and/or histologic extracapsular extension of melanoma in clinically (macroscopic) involved node(s), ≥1 parotid node, ≥2 cervical or axillary nodes, ≥3 inguinofemoral nodes, ≥3 cm cervical or axillary node, and/or ≥4 cm inguinofemoral node.[13,15,16]**
  - **Dosing Regimens: Optimal regional nodal doses are not well established, but potential regimens include:[a,17]**
    - **50–66 Gy in 25–33 fractions over 5–7 weeks[18,19]**
    - **48 Gy in 20 fractions over 4 weeks[13]**
    - **30 Gy in 5 fractions over 2 weeks (twice per week or every other day)[12]**

- **Definitive or Palliative Therapy for Regional Metastases**
  - **Definitive or palliative intent radiation can also be considered for:**
    - **Unresectable nodal, satellite, or in-transit disease**
    - **Residual local, satellite, or in-transit disease after prior treatment**
  - **Dosing Regimens: Optimal doses are not established, but potential regimens include[a]:**
    - **24–27 Gy in 3 fractions over 1–1.5 weeks[20,21]**
    - **32 Gy in 4 fractions over 4 weeks[22]**
    - **40 Gy in 8 fractions over 4 weeks[21]**
    - **50 Gy in 20 fractions over 4 weeks[22]**
    - **30 Gy in 10 fractions over 2 weeks[23]**
    - **30 Gy in 5 fractions over 2 weeks**
    - **20 Gy in 5 fractions over 1 week[23]**
    - **8 Gy in 1 fraction over 1 day[23]**

[a]Hypofractionated regimens may increase the risk for long-term complications.

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Continued
References

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Distant Metastatic Disease

- **Brain Metastases**
  - Stereotactic radiosurgery (SRS) and fractionated stereotactic RT (SRT) are techniques for delivering a high dose of radiation to a specific target while delivering a minimal dose to surrounding tissues, generally in the brain and spine and in 1 to 5 sessions. IGRT should be used to improve accuracy of radiotherapy delivery, where clinically appropriate.
  - SRS or SRT as primary treatment
    - ◊ Smaller tumors may be treated with maximal doses of 15–24 Gy in 1 fraction according to volume guidelines based on maximum tolerated dose results from the RTOG 90-05 dose escalation study (shown below).[24] Caution is recommended for lesions >3 cm, and single-fraction radiosurgery is not typically recommended for lesions >4 cm.
      - – Lesions with maximum diameter ≤20 mm receive up to 24 Gy
      - – Lesions with maximum diameter 21–30 mm receive up to 18 Gy
      - – Lesions with maximum diameter 31–40 mm receive up to 15 Gy
    - ◊ Larger tumors, however, may be treated with fractionated SRT. Potential regimens include, but are not limited to:[25,26]
      - – 24–27 Gy in 3 fractions
      - – 25–35 Gy in 5 fractions
  - SRS/SRT as adjuvant treatment
    - ◊ Smaller cavities may be treated with single-fraction SRS maximal doses ranging from 12–20 Gy depending on cavity volume per the NCCTG N107C trial protocol.[27]
      - – Lesions <4.2 cc receive 20 Gy
      - – Lesions ≥4.2 cc to <8.0 cc receive 18 Gy
      - – Lesions ≥8.0 cc to <14.4 cc receive 17 Gy
      - – Lesions ≥14.4 cc to <20 cc receive 15 Gy
      - – Lesions ≥20 cc to <30 cc receive 14 Gy
      - – Lesions ≥30 cc to <5 cm receive 12 Gy
    - ◊ In general, single-fraction adjuvant SRS is not recommended for cavities >5 cm.
    - ◊ Larger cavities, however, may be treated with fractionated SRT. Potential regimens include, but are not limited to:
      - – 24–27 Gy in 3 fractions
      - – 25–35 Gy in 5 fractions
  - Palliative whole brain RT (WBRT) (See ME-16)
    - ◊ Only consider for palliative purposes when SRS/SRT is not feasible in patients with good performance status for whom effective systemic therapy has failed (See ME-L).
    - ◊ The pros and cons of WBRT should be considered carefully in the context of individual patient preferences/goals of care.[28]
    - ◊ WBRT can be considered if radiographic, clinical, or pathologic signs of leptomeningeal carcinomatosis are present (see LEPT-1 in the NCCN Guidelines for Central Nervous System Cancers).
    - ◊ Common WBRT regimens include:
      - – 30 Gy in 10 fractions over 2 weeks
      - – 37.5 Gy in 15 fractions over 3 weeks
      - – 20 Gy in 5 fractions over 1 week
  - Adjuvant WBRT
    - ◊ Adjuvant WBRT after resection or SRS/SRT is not recommended for patients with melanoma.[29]
      - – Recent data from a randomized trial suggest that adjuvant WBRT is associated with worse cognitive decline when compared to adjuvant SRS/SRT alone.[27] Although local control appears superior with adjuvant WBRT, there were no differences in OS.
    - ◊ For dosing, see Palliative WBRT section above.
  - Also see NCCN Guidelines for Central Nervous System Cancers.

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Continued
References

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Distant Metastatic Disease (continued)

- **Palliative Treatment of Symptomatic Extracranial Metastases**
  - **A variety of treatment regimens are acceptable depending on location and/or clinical indication. Higher doses and/or hypofractionated regimens may be associated with more durable palliation.[30,31]**
  - **Potential regimens include:**
    - ◊ **24–27 Gy in 3 fractions over 1–1.5 weeks[20,21]**
    - ◊ **32 Gy in 4 fractions over 4 weeks[22]**
    - ◊ **40 Gy in 8 fractions over 4 weeks[21]**
    - ◊ **50 Gy in 20 fractions over 4 weeks[22]**
    - ◊ **30 Gy in 10 fractions over 2 weeks[23]**
    - ◊ **30 Gy in 5 fractions over 2 weeks**
    - ◊ **36 Gy in 6 fractions over 2 weeks**
    - ◊ **20 Gy in 5 fractions over 1 week[23]**
    - ◊ **8 Gy in 1 fraction over 1 day[23]**

- **Ablative Treatment for Intact Extracranial Metastases**
  - **Higher doses utilizing conformal techniques such as stereotactic body RT (SBRT) may offer more durable local control.[32]**
  - **SBRT may be considered for selected patients with oligometastasis.[32]**
  - **This must be weighed against potential toxicities, and strict adherence to normal tissue constraints is recommended.**
  - **Spine SBRT regimens include but are not limited to:**
    - ◊ **16–24 Gy in 1 fraction over 1 day[31]**
    - ◊ **20–24 Gy in 2 fractions over 1 week[33]**
    - ◊ **24–27 Gy in 3 fractions over 1 week[34]**
    - ◊ **25–30 Gy in 5 fractions over 2 weeks**
  - **SBRT regimens for other body sites include but are not limited to:**
    - ◊ **48–60 Gy in 3 fractions over 1 week[32,35]**
    - ◊ **40–60 Gy in 4–5 fractions over 2 weeks[32,36]**
    - ◊ **16–24 Gy in 1 fraction over 1 day[31]**

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Continued
References

PRINCIPLES OF RADIATION THERAPY FOR MELANOMA

Managing Systemic Therapy During Radiation

- **Interactions between RT and systemic therapies need to be very carefully considered as there is potential for increased toxicity, particularly when utilizing higher doses of radiation.[37-39]**
- **BRAF and/or MEK inhibitors may interact with radiation and can lead to increased CNS, pulmonary, dermatologic, and visceral toxicity.[40,41]Consideration should be given to holding BRAF and/or MEK inhibitors ≥3 days before and after fractionated RT and ≥1 day before and after SRS (or other high-dose-per-fraction regimens).[42]**
- **Several studies have explored the potential interaction between immunotherapy and RT. These studies have not found clear evidence that consistent adverse interactions exist.[38,39,43-45]**

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PRINCIPLES OF RADIATION THERAPY FOR MELANOMA
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PRINCIPLES OF RADIATION THERAPY FOR MELANOMA
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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE[a,b]

FIRST-LINE THERAPY[c]

Metastatic or unresectable disease →

- Preferred regimens
  - Anti PD-1 monotherapy[d,e]
    - ◊ Pembrolizumab (category 1)
    - ◊ Nivolumab (category 1)
  - Nivolumab/ipilimumab (category 1)[d,e,f]
  - Combination targeted therapy if *BRAF* V600-activating mutation[g,h,i,j]
    - ◊ Dabrafenib/trametinib (category 1)
    - ◊ Vemurafenib/cobimetinib (category 1)
    - ◊ Encorafenib/binimetinib (category 1)
- Other recommended regimens
  - Pembrolizumab/low-dose ipilimumab[k] (category 2B)
  - Combination targeted therapy and immunotherapy if *BRAF* V600-activating mutation present[d,g,h]
    - ◊ Vemurafenib/cobimetinib + atezolizumab[l]
    - ◊ Dabrafenib/trametinib + pembrolizumab (category 2B)[m]

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

SECOND-LINE OR SUBSEQUENT THERAPY[n]

- Systemic therapy
  - Preferred regimens
    - ◊ Anti PD-1 monotherapy[d,e]
      - – Pembrolizumab
      - – Nivolumab
    - ◊ Nivolumab/ipilimumab[d,e,f]
    - ◊ Pembrolizumab/low-dose ipilimumab for tumors that have progressed after prior anti-PD-1 therapy[d,e]
    - ◊ Combination targeted therapy if *BRAF* V600-activating mutation[h,i,j]
      - ▪ Dabrafenib/trametinib
      - ▪ Vemurafenib/cobimetinib
      - ▪ Encorafenib/binimetinib
  - Other regimens
    - ◊ Ipilimumab[d]
    - ◊ High-dose IL-2[o]
  - Useful in certain circumstances
    - ◊ Ipilimumab[d]/intralesional T-VEC (category 2B)
    - ◊ Cytotoxic agents[p]
    - ◊ Imatinib for tumors with activating mutations of *KIT*
    - ◊ Larotrectinib or entrectinib for *NTRK* gene fusion-positive tumors
    - ◊ Binimetinib for *NRAS*-mutated tumors that have progressed after prior immune checkpoint inhibitor therapy[q] (category 2B)
- Consider best supportive care for poor performance status (See NCCN Guidelines for Palliative Care)

See footnotes on next page

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

FOOTNOTES FOR SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE

[a] See Principles of Imaging --Treatment Response Assessment (ME-D).

[b] See Systemic Therapy Considerations (ME-J).

[c] The choice of a treatment is based on evaluation of the individual patient.

[d] See NCCN Guidelines for Management of Immunotherapy-Related Toxicities for proactive monitoring and management of toxicities in patients undergoing treatment with immune checkpoint inhibitors.

[e] Testing for tumor PD-L1 should not guide clinical decision-making. The utility of this biomarker requires further investigation.

[f] Nivolumab/ipilimumab combination therapy is associated with improved ORR, PFS, and OS compared with single-agent ipilimumab, at the expense of significantly increased toxicity. Compared to nivolumab, the impact of nivolumab/ipilimumab combination therapy on OS is not known. The phase III trial of nivolumab/ipilimumab or nivolumab monotherapy versus ipilimumab monotherapy was conducted in previously untreated patients with unresectable stage III or IV melanoma. Relative indications for combination nivolumab/ipilimumab in comparison to PD-1 monotherapy include: patient willingness to take on high risk of treatment-related toxicities (immune-related adverse events [irAEs]); absence of comorbidities or autoimmune processes that would elevate the risk of irAEs; and patient social support and anticipated compliance with medical team to handle toxicities.

[g] Positive VE1 IHC results are sufficient for starting targeted therapy in patients who are symptomatic or have rapidly progressing disease. Confirmatory *BRAF* molecular testing is encouraged. See Principles of Molecular Testing (ME-C).

[h] See Management of Toxicities Associated with Targeted Therapy (ME-K).

[i] In previously untreated patients with unresectable AJCC 7th Edition stage IIIC or stage IV disease, BRAF/MEK inhibitor combination therapy was associated with improved response rate, PFS, and OS compared to BRAF inhibitor monotherapy.

[j] If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF inhibitor monotherapy is an option, especially in patients who are not appropriate candidates for checkpoint immunotherapy.

[k] Dosing used in KEYNOTE-029: Pembrolizumab 2 mg/kg IV plus ipilimumab 1 mg/kg IV every 3 weeks (Q3W) for four doses, followed by pembrolizumab 2 mg/kg Q3W for up to 2 years or disease progression, intolerable toxicity, withdrawal of consent, or investigator decision.

[l] In a randomized, double-blind, placebo-controlled, phase 3 trial, the addition of atezolizumab to vemurafenib and cobimetinib was associated with longer median PFS and longer duration of response; however, the triplet induced more toxicity than the vemurafenib/cobimetinib doublet. Until mature OS data are published, it is not clear that the triplet regimen is preferred over sequential BRAF/MEK inhibitor therapy followed by PD-L1 or PD-1 inhibition.

[m] The triplet of dabrafenib, trametinib, and pembrolizumab was associated with longer median PFS and 24-month PFS compared to the doublet of dabrafenib and trametinib; however, grade 3–5 treatment-related adverse events occurred in 58% of patients (including one death from pneumonitis) in the triplet arm and 25% of patients in the doublet arm.

[n] For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and if from a different class. For patients who progressed on single-agent anti-PD-1 checkpoint immunotherapy, anti-PD-1/ipilimumab combination therapy or ipilimumab monotherapy is a reasonable treatment option. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered.

[o] 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.

[p] For cytotoxic therapy recommendations, see (ME-I 3 of 7).

[q] In patients who were previously untreated or had prior failure of immunotherapy, binimetinib was associated with a response rate of 15%, and demonstrated a modest improvement in PFS with no improvement in OS compared with single-agent dacarbazine.

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OTHER SYSTEMIC THERAPIES[b]

Cytotoxic Therapy for Metastatic Disease (useful in certain circumstances)

- **In general, immunotherapy and targeted therapy are preferred for treatment of unresectable or distant metastatic disease.**
- **For patients who are not eligible for any of the recommended immunotherapy or targeted therapy options (due to progression on prior therapy, unacceptable toxicity, or comorbidities), cytotoxic therapy can be considered on a case-by-case basis, and is therefore considered useful in certain circumstances.**
- **The literature is not directive regarding the specific chemotherapeutic agent(s), and none of these regimens offers superior outcomes, or has been shown to improve OS in a randomized phase III trial setting. However, the literature does provide evidence that some patients experience tumor regression (usually temporary) after cytotoxic therapy.**
- **Cytotoxic agents that have been used alone or in combination include (but are not limited to): dacarbazine, temozolomide, paclitaxel, albumin-bound paclitaxel, carboplatin/paclitaxel, and cisplatin/vinblastine/dacarbazine (CVD) (category 2B for CVD).**

[b] See Systemic Therapy Considerations (ME-J).

Continued

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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE
REFERENCES

Immunotherapy

Pembrolizumab

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Nivolumab

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Ipilimumab

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Continued

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SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE
REFERENCES

Immunotherapy (continued)

Nivolumab/Ipilimumab

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Ipilimumab/intralesional T-VEC

- Chesney J, Puzanov I, Collichio F, et al. Randomized, open-label phase II study evaluating the efficacy and safety of talimogene laherparepvec in combination with ipilimumab versus ipilimumab alone in patients with advanced, unresectable melanoma. J Clin Oncol 2018;10;36:1658-1667.

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OTHER SYSTEMIC THERAPIES 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.
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Vemurafenib/Cobimetinib + Atezolizumab

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Dabrafenib/trametinib + pembrolizumab

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Encorafenib/Binimetinib

- Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2018;19:603-615.
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OTHER SYSTEMIC THERAPIES - REFERENCES

Targeted Therapy (Single-Agent Therapy) (continued)

Vemurafenib

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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

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Paclitaxel/carboplatin

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SYSTEMIC THERAPY CONSIDERATIONS

General Principles

- Treatment decisions need to be individualized based upon patient goals and anticipated therapy tolerance. Some general principles are outlined below.
- Response and duration of benefit are influenced by burden of disease when using targeted or immune therapies.
- For patients whose tumor harbors a *BRAF* mutation and who would benefit from a more rapid response, BRAF/MEK inhibition may be preferred.

Considerations for Selection of Systemic Therapy for Unresectable or Metastatic Disease

- Randomized clinical trials are ongoing to compare front-line systemic targeted therapy (BRAF/MEK) to immune therapy with checkpoint inhibitors. Results will help define the best approach for initial therapy.

▸ Considerations for deciding between anti-PD-1/ipilimumab combination versus anti-PD-1 alone
- ◊ Both anti-PD-1 monotherapy and anti-PD-1/ipilimumab combination therapy may provide durable disease control.
- ◊ Combination therapy is associated with higher clinical response rates, PFS and OS, and a reduced need for subsequent therapy, at the expense of more frequent and more severe immune-related adverse events.
- ◊ Thus, combination therapy may be preferred in patients with good performance status when appropriate clinical support is readily available (see NCCN Guidelines for Management of Immunotherapy-Related Toxicities).

▸ Considerations for anti-PD-1/ipilimumab dosing and anti-PD-1 monotherapy dosing
- ◊ The clinical response to FDA-approved anti-PD-1 dosing schedules appears similar, although comparative trials are not available. The choice of regimen may vary based upon the physician's preference for patient monitoring and the patient's schedule.
- ◊ The use of ipilimumab 3 mg/kg with nivolumab 1 mg/kg every 3 weeks for 4 doses with subsequent consideration for nivolumab monotherapy is an FDA-approved regimen.
- ◊ An alternative regimen utilizing ipilimumab 1 mg/kg and nivolumab 3 mg/kg every 3 weeks for 4 doses, with subsequent consideration for nivolumab monotherapy, is associated with lower rates of immune-mediated toxicity; however, the long-term efficacy and durability of this alternative less toxic regimen remain to be defined.
- ◊ Alternative dosing can be utilized for patients in whom there is increased concern regarding ability to tolerate immune-related adverse events.
- ◊ The initial clinical trials and FDA approvals of pembrolizumab and nivolumab in 2014 used dosing based on patient weight (2 mg/kg every 3 weeks for pembrolizumab and 3 mg/kg every 2 weeks for nivolumab). Subsequently the FDA amended dosing to flat doses (200 mg or 400 mg every 3 or 6 weeks, respectively, for pembrolizumab, or 240 mg or 480 mg every 2 or 4 weeks, respectively, for nivolumab), which are safe and efficacious. However, substantial cost savings for pembrolizumab and nivolumab may be obtained by weight-based dosing, depending on patient weight and on institutional practices regarding vial sharing.

▸ Considerations for selecting among the three BRAF/MEK inhibitor options
- ◊ Comparative studies are not available to select between the BRAF/MEK combination therapy agents.
- ◊ Toxicity may require dose/schedule modifications (See Management of Toxicities Associated with Targeted Therapy, ME-K).

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Continued

SYSTEMIC THERAPY CONSIDERATIONS

Considerations for Patients with CNS Disease

- For treatment planning in patients with CNS disease, consider prioritizing systemic therapies that have been shown to have activity in CNS metastases.
- For systemic therapy in patients with asymptomatic brain metastasis not requiring corticosteroids, combination therapy with anti-PD-1/ipilimumab is preferred in comparison to anti-PD-1 monotherapy or dabrafenib plus trametinib due to superior intracranial activity.
- The treatment plan for patients with brain metastases should be coordinated with the radiation oncology team even when radiation is not initially utilized.
- For patients with symptomatic brain lesions or who require corticosteroids for symptom control, management by a multidisciplinary team, including neurosurgery, radiation oncology, medical oncology, and palliative care, is strongly recommended.

When to Stop or Switch Therapies

- Definition of maximal clinical benefit
  - Patients who achieve a clinical response following combination immune therapy and who have experienced immune-related adverse events (grade 3 or higher) and receive no further treatment do similarly well compared to patients who continue on to maintenance anti-PD-1 treatment.
  - The optimal duration of anti-PD-1 therapy remains unknown.
  - Most patients who achieve a complete or partial response and discontinue anti-PD-1 monotherapy after 2 years of therapy maintain the response with 2 years of follow-up.

- Defining response and pseudoprogression
  - Radiographic or clinically evident increase in tumor size may precede regression early in the course of immune-based therapy (pseudoprogression).
  - As the average time to response varies between 6 and 12 weeks depending upon the therapy, it is reasonable to continue immunotherapy for an additional treatment interval (6–10 weeks) in some patients with tumor growth who are tolerating therapy and doing well clinically.
  - Continued growth 16 weeks after starting immunotherapy should be considered true progression.

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Continued

SYSTEMIC THERAPY CONSIDERATIONS

Recommendations for Patients Who Progress on Systemic Therapy

- ***BRAF*** **V600-activating mutation present:**
  - **For patients who progress on immune therapy, options include the following (if not already received):**
    - ◊ **BRAF/MEK inhibitor combination therapy**
    - ◊ **Combination immune therapy, options include:**
      - – **Anti-PD-1/ipilimumab (preferred)**
      - – **T-VEC/ipilimumab therapy (for low burden of disease and injectable lesions)**
    - ◊ **Ipilimumab monotherapy (if prior progression on single-agent anti-PD-1 therapy)**
    - ◊ **Clinical trials**
  - **For patients who progress following BRAF/MEK inhibitor combination therapy, consider the following options (if not previously received):**
    - ◊ **Combination immune therapy, options include:**
      - – **Anti-PD-1/ipilimumab**
      - – **T-VEC/ipilimumab therapy (for low burden of disease and injectable lesions)**
    - ◊ **Single-agent anti-PD-1**
    - ◊ **Clinical trials**
  - **Some patients who previously demonstrated a clinical benefit to BRAF/MEK inhibition may benefit from rechallenge with BRAF/MEK inhibitors after other intervening therapies. The optimal time interval between initial treatment and retreatment with BRAF/MEK to expect further clinical benefit has not been defined.**
  - **For patients who progress on BRAF/MEK inhibitor combination therapy, anti-PD-1 therapy, and ipilimumab (in combination with anti-PD-1 or sequentially), consider the following options:**
    - ◊ **Clinical trials**
    - ◊ **T-VEC (for low burden of disease and injectable lesions)**
    - ◊ **High-dose bolus IL-2**
    - ◊ **Cytotoxic chemotherapy**
    - ◊ **Best supportive care**

- ***BRAF*** **V600-activating mutation not present:**
  - **For patients with progression on immune therapy, consider the following options (if not already received):**
    - ◊ **Combination immune therapy, options include:**
      - – **Clinical trials**
      - – **Anti-PD-1/ipilimumab (preferred)**
      - – **T-VEC/ipilimumab therapy (for low burden of disease and injectable lesions)**
    - ◊ **Ipilimumab monotherapy (if prior progression on single-agent anti-PD-1 therapy).**
  - **For patients with progression on anti-PD-1 and ipilimumab (in combination with anti-PD-1 or sequentially), consider the following options:**
    - ◊ **Clinical trials**
    - ◊ **T-VEC (for low burden of disease and injectable lesions)**
    - ◊ **High-dose bolus IL-2**
    - ◊ **Cytotoxic chemotherapy**
    - ◊ **Best supportive care**

Use of High-Dose IL-2 in Select Patients

- **IL-2 may be used in patients who would be anticipated to tolerate therapy as assessed by an experienced treating physician**
- **IL-2 use should be limited to centers and providers with prior delivery of IL-2**
- **IL-2 can give durable responses in a subset of patients**
- **IL-2 activity and safety data are limited for patients who have progressed on available therapies (eg, immune checkpoint inhibitors)[1]**

[1]Buchbinder EI, Dutcher JP, Daniels GA, et al. Therapy with high-dose Interleukin-2 (HD IL-2) in metastatic melanoma and renal cell carcinoma following PD1 or PDL1 inhibition. J Immunother Cancer 2019;7:49.

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

Continued

SYSTEMIC THERAPY CONSIDERATIONS

Use of Cytotoxic Agents for Unresectable or Distant Metastatic Disease

- Appropriate context for use of cytotoxic agents
  - Cytotoxic agents may be used in patients who are not candidates for further standard, immune-based, BRAF/MEK inhibitor, or clinical trial-directed therapy and who have symptomatic cancer.
  - While response rates and toxicity differ across cytotoxic agents, the impact on OS is limited.

- Considerations for cytotoxic agents
  - Among the recommended cytotoxic options, combination of carboplatin and paclitaxel or single-agent temozolomide are preferred.
  - Other agents include dacarbazine, paclitaxel, albumin-bound paclitaxel, or cisplatin/vinblastine/dacarbazine (CVD) (category 2B for CVD).
  - Multiagent chemotherapy has shown a marginal improvement in response rate with no difference in OS when compared with single-agent dacarbazine.

Considerations for Selection of Adjuvant Systemic Therapy

- Deciding between systemic therapy versus observation
  - Both targeted agents (dabrafenib/trametinib) and anti-PD-1 therapies have shown improvement in RFS (both options preferred), but the impact of early (adjuvant) versus late (at time of recurrence) treatment on OS remains undefined.
  - Thus, for high-risk patients, observation alone remains an option.
  - In patients with a low risk of recurrence (for example, stage IIIA with <1 mm of nodal tumor burden), observation is preferred; although adjuvant systemic therapy is FDA approved for these patients, they were excluded from the prospective adjuvant therapy trials.

- Considerations for selecting among adjuvant systemic therapies
  - Side effects from immune checkpoint inhibitor therapy tend to be longer lasting than those from BRAF/MEK inhibitor therapy, persisting after discontinuation of treatment.
  - Whereas BRAF/MEK inhibitor therapy is orally administered, immune checkpoint inhibitors are parenterally administered.
  - Patient history, including pre-existing autoimmune disease, or other conditions that would be exacerbated by toxicities associated with therapy, should be considered.
  - There is no good evidence basis for selection between adjuvant BRAF/MEK inhibitors versus immune checkpoint inhibitors, as both have similar efficacy. Some clinicians prefer immune checkpoint inhibitors based on the presumption that these provide more durable benefit, but there is no high-quality evidence to support this.
  - Due to high rates of associated toxicity, adjuvant ipilimumab monotherapy has largely been replaced by adjuvant anti-PD-1 therapy. There are very few settings in which single-agent adjuvant ipilimumab is appropriate. The rare scenario in which adjuvant ipilimumab may be appropriate would be in patients who have prior exposure to anti-PD-1 therapy, especially if the patient experienced progression or recurrence on prior anti-PD-1 therapy.
  - Ipilimumab (10 mg/kg) demonstrated an improvement in OS compared to placebo, although its toxicity precludes this from being a preferred option.
  - Ipilimumab (3 mg/kg) is the recommended dose. This regimen appears to result in a similar disease-free survival benefit as adjuvant high-dose ipilimumab, but with fewer and less severe adverse events.

Note: All recommendations are category 2A unless otherwise indicated.
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MANAGEMENT OF TOXICITIES ASSOCIATED WITH 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.**
  - **Severe skin toxicity (eg, drug-induced hypersensitivity syndrome) can occur with the use of BRAF inhibitors following immune checkpoint blockade, and requires prompt dermatologic consultation for accurate diagnosis and treatment.1**
- **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 inhibitor monotherapy (~20%).[a] 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 BRAF/MEK inhibitor combination at the onset of pyrexia will often interrupt the episode, and treatment can be resumed with full-dose BRAF/MEK inhibitors upon cessation of pyrexia and pyrexia-related symptoms. Upon re-exposure to BRAF/MEK inhibitors, 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 BRAF/MEK inhibitors, 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, vemurafenib with or without cobimetinib, or encorafenib with or without binimetinib and for the management of these toxicities, see the full prescribing information (http://www.accessdata.fda.gov/scripts/cder/daf).**

Footnotes

[a]The frequency of pyrexia and other adverse events varies between specific BRAF/MEK inhibitor combinations.

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[1]Lamiaux M, Scalbert C, Lepesant P, et al. Severe skin toxicity with organ damage under the combination of targeted therapy following immunotherapy in metastatic melanoma. Melanoma Res 2018;28:451-457.

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PRINCIPLES OF BRAIN METASTASES MANAGEMENT

Selection of Initial Treatment Modality (Brain-Directed vs. Systemic)

- **Multidisciplinary evaluation (ie, neurosurgery, radiation oncology, medical oncology) prior to initiation of treatment is strongly recommended.**

- **As a general approach, patients who present with a higher burden of intracranial disease associated with symptoms will often require local management. In patients with lower volume, asymptomatic brain metastases as well as those with extensive extracranial disease, an initial course of systemic therapy may be preferred. It is likely that many patients presenting with brain metastases will need both systemic therapy and local brain-directed therapy over their course of treatment.**

- **The selection of initial treatment modality depends on a combination of clinical factors. Those factors determined to be most important are included below:**
  - **The extent of intracranial disease, including factors such as the size, number, and location of metastases guides the initial treatment of brain metastases.**
    - **There are limited data supporting the efficacy of upfront systemic therapy in patients with symptomatic brain metastases,[1-6] and brain-directed therapy is generally preferred.**
    - **In patients with other high-risk clinical scenarios (eg, hemorrhage, eloquent cortex, brainstem), brain-directed therapy may be preferred over systemic therapy.**
  - **The burden of extracranial disease will affect initial treatment selection. In patients with extensive extracranial disease, prompt initiation of systemic therapy may be preferred.**
  - **The context in which the brain metastases developed should be considered when selecting initial treatment. In patients who develop brain metastases while on systemic therapy, brain-directed therapy may be preferred.**

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

Continued

PRINCIPLES OF BRAIN METASTASES MANAGEMENT

Brain-Directed Therapy

- **Surgery versus radiation**
  - **Surgery is the preferred option for large, symptomatic lesions or single lesions in resectable areas, particularly when there is diagnostic uncertainty or when additional tissue sampling may drive future therapeutic decisions.**
    - ◊ **Postoperative radiation to the resection cavity may be considered to decrease the risk of local recurrence.[7]**
    - ◊ **Adjuvant WBRT is not recommended after resection for melanoma brain metastases.**
  - **SRS is the preferred radiation modality for melanoma brain metastases and can be delivered to multiple lesions depending on local experience and technology.**
    - ◊ **Large lesions should be treated with fractionated SRS (3–5 fractions) to decrease the risk of radionecrosis.**
    - ◊ **Adjuvant WBRT is not recommended after SRS/SRT for melanoma brain metastases.**
  - **Palliative WBRT**
    - ◊ **Only recommended for palliative purposes when SRS/SRT is not feasible in patients with good performance status for whom effective systemic therapy has failed.**
    - ◊ **WBRT delivers a lower dose of radiation to metastases in the brain and is associated with lower local control and increased risk of late neurocognitive impairment.**
    - ◊ **For patients receiving WBRT, hippocampal avoidance and memantine should be considered to reduce neurocognitive toxicity in eligible patients.[8]**
- **For a detailed discussion of radiation dosing and options: See Principles of Radiation (ME-H).**

- **Management of symptoms**
  - **For patients who are symptomatic from their intracranial tumor burden, corticosteroids remain the mainstay of therapy.**
    - ◊ **Patients should be on the lowest dose possible to control symptoms with a plan to taper if intracranial disease responds to therapy.**
    - ◊ **The impact of corticosteroids on the efficacy of future or current immunotherapy should be considered and weighed against the severity of symptoms.**
  - **Patients who present with seizures should be treated with standard first-line anticonvulsant drug therapy.**
    - ◊ **Close monitoring of serum levels and use of the lowest effective dose is recommended to minimize toxicity.**
    - ◊ **Prophylactic anticonvulsant drug therapy in a patient with no known seizure history is generally not recommended due to the adverse side effect profile of medical therapies.[9,10] However, as hemorrhage is associated with increased risk of seizure, selected patients with large bleeding lesions could be considered for prophylactic anticonvulsants.**
  - **For symptomatic lesions following SRS that are not responsive to corticosteroids, consider neurosurgical evaluation for both diagnosis and therapy.**
    - ◊ **If unresectable, a short course of bevacizumab may allow improvement in overall quality of life by reducing steroid dose and improving functional status.**
  - **In other scenarios, bevacizumab may also be used as a means to lower steroid dose in patients who are refractory to steroid withdrawal.**
    - ◊ **If clinically feasible, allow bevacizumab washout for at least 2 weeks before surgery. See Medical Management (BRAIN-E 2 of 3) from the NCCN Guidelines for Central Nervous System Cancers.**

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Continued

PRINCIPLES OF BRAIN METASTASES MANAGEMENT

Systemic Therapy

- Some patients may be candidates for systemic therapy as the sole initial treatment modality, with no need for brain-directed therapy (surgery or RT) unless there is intracranial progression.
- For all patients treated with this approach, close surveillance (brain MRI every 6–8 weeks) is strongly recommended.

***Patients who are most likely to be considered for systemic therapy as the sole initial treatment modality include*:**

- Patients with <3 cm asymptomatic brain metastases, not requiring corticosteroids, and no prior treatment with systemic therapy.
  - The clinical trial supporting this strategy utilized nivolumab/ipilimumab and found high intracranial response rates in patients with previously untreated brain metastases, which appear to be durable.
    - Systemic corticosteroids may interfere with the efficacy of nivolumab/ipilimumab and should be avoided in patients being considered for combination nivolumab/ipilimumab.
  - For patients who are not candidates for nivolumab/ipilimumab combination therapy:
    - Single-agent anti-PD-1 therapies have been shown to have only modest intracranial activity, and are not preferred as the initial treatment modality for treatment of brain metastases in most patients.
    - Consider early brain-directed therapy.
    - Consider BRAF/MEK inhibitor combination therapy in patients with *BRAF* V600-activating mutation.
- Select symptomatic patients with *BRAF*-mutated melanoma, who have not been previously treated with a BRAF/MEK inhibitor.
  - BRAF/MEK inhibitors result in a high intracranial response rate; however, PFS is shorter than reported data for extracranial disease. As such, this approach may be most useful when patients also have a large burden of extracranial disease or numerous brain metastases not amenable to local therapy.
  - Patients treated with this approach are very likely to need subsequent brain-directed therapy, and should be monitored closely.
  - See Systemic Therapy for Unresectable or Metastatic Disease (ME-I) for recommended BRAF/MEK inhibitor combinations.

Adjuvant Therapy After Resection of Brain Metastases

- Following resection of brain metastases, adjuvant radiation to the cavity may be considered.[7]
- Patients rendered NED from following resection of brain metastases may be considered for adjuvant systemic therapy.
  - There are no data to guide selection of the optimal adjuvant systemic therapy in patients rendered NED by brain directed-treatment (See ME-16 for adjuvant systemic therapy options for resected stage IV disease).

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Continued

PRINCIPLES OF BRAIN METASTASES MANAGEMENT

Integration of Systemic Therapies with Brain-Directed Therapies

- **Many patients with melanoma brain metastases will require a combined modality approach. As described above, the choice and sequencing of therapy depends on a number of clinical factors.**
  - **For patients who are on BRAF/MEK inhibitor combination therapy and RT is determined to be appropriate, it is recommended to hold therapy 1 day before and after SRS, and at least 3 days before and after fractionated RT.[11]**
  - **Limited data are available, but currently there does not appear to be a concerning safety signal with the combination of RT and immune checkpoint inhibitors.**
  - **In select patients who are otherwise continuing to benefit from systemic therapy, local treatment for the brain metastases and continuation of the same systemic therapy can be considered.**

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

Continued

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

Table 1. **American Joint Committee on Cancer (AJCC) Definitions for T, N, M**

T Category	Thickness	Ulceration Status
TX: Primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8–1.0 mm	With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0–4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Continued

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Table 1. **American Joint Committee on Cancer (AJCC) Definitions for T, N, M (*continued*)**

Extent of Regional Lymph Node and/or Lymphatic Metastasis

N Category	Number of Tumor-Involved Regional Lymph Node	Presence of In-Transit, Satellite, and/or Microsatellite Metastases
NX	Regional nodes not assessed (eg, SLN biopsy not performed, regional nodes previously removed for another reason) Exception: When there are no clinically detected regional metastases in a pT1 cM0 melanoma, assign cN0 instead of pNX	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes	
N1a	One clinically occult (ie, detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (ie, detected by SLN biopsy)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes
N3	Four or more tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (ie, detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Continued

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M Category	Anatomic Site	LDH Level
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

- Serum lactate dehydrogenase (LDH)
- Suffixes for M category: (0) LDH not elevated, (1) LDH elevated.
- No suffix is used if LDH is not recorded or is unspecified.

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Table 2. **AJCC Prognostic Stage Groups**

Clinical Staging (cTNM)*

	T	N	M
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	Any T, Tis	≥N1	M0
Stage IV	Any T	Any N	M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastasis also are included. Note there is only one stage group for clinical Stage III melanoma.

Pathological Staging (pTNM)**

	T	N	M
Stage 0†	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	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	T1a/b, T2a	N1a, N2a	M0
Stage IIIB	T0	N1b, N1c	M0
	T1a/b, T2a	N1b/c, N2b	M0
	T2b, T3a	N1a/b/c, N2a/b	M0
Stage IIIC	T0	N2b/c, N3b/c	M0
	T1a/b, T2a/b, T3a	N2c, N3a/b/c	M0
	T3b, T4a	Any N ≥ N1	M0
	T4b	N1a/b/c, N2a/b/c	M0
Stage IIID	T4b	N3a/b/c	M0
Stage IV	Any T, Tis	Any N	M1

**Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide-excision (surgical) specimen that constitutes primary tumor surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.

†Pathological Stage 0 and pathological T1 without clinically detected regional or distant metastases (pTis/pT1 cN0 cM0) do not require pathological evaluation of lymph nodes to complete pathological staging; use cN0 to assign pathological stage.

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

All recommendations are category 2A unless otherwise indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Discussion

This discussion corresponds to the NCCN Guidelines for Melanoma: Cutaneous. The following sections were last updated on March 12, 2019: Adjuvant Systemic Therapy for Melanoma, Treatment for Unresectable Stage III or Distant Metastatic Disease (Stage IV). The rest was last updated on July 7, 2016.

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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 (SLN) 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 SLNs.[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 SLN 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 SLN, 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 SLN 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 SLN 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 SLN 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] SLN 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 N	Positive SLN n	Positive SLN %
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)

Study	Primary Tumor Thickness <0.75 mm Positive SLN n/N	%	Primary Tumor Thickness 0.75–1.0 mm Positive SLN 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 SLN. 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-SLNs (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 SLNs (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 SLN, 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 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. [340] Another retrospective study of patients with resected recurrent desmoplastic melanoma (n = 130) also showed that adjuvant RT was associated with improved local control but not distant metastasis-free survival (DMFS).[341] 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 (RFS) in patients who received RT in addition to surgery.[342] Results from these four and one smaller retrospective study[343] 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).[344]

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.[345] 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.[346,347] One retrospective analysis suggested that the benefit of RT for regional control may be associated with doses of at least 50 Gy.[348] 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.[349] 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.[350] Patients were treated with lymphadenectomy followed by either adjuvant radiation (48 Gy in 20 fractions) to the nodal basin or observation.[349] 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.[349] Although not primary endpoints, RFS and OS showed no statistically significant differences for patients treated with adjuvant RT versus observation. Adjuvant radiation was associated with frequent grade 2 to 4 toxicities primarily affecting the skin or subcutaneous tissue, but also including pain, nerve damage, and joint adverse events (AEs).

Various fractionation schemes for postoperative adjuvant radiation have been evaluated in retrospective studies.[340,351-355] 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.[356-362] 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.[362] 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.[363,364] 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.[350] 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*.

Adjuvant Systemic Therapy for Melanoma

Brief History of Adjuvant Therapy Options for Melanoma

For adjuvant treatment of melanoma in patients rendered free of disease by surgery, traditional systemic therapy approaches have proven to be ineffective. Adjuvant interferon alfa (IFN alfa), particularly high-dose IFN alfa, has been widely used in patients with melanoma for many years. A large body of clinical evidence has amassed from prospective randomized trials comparing adjuvant IFN alfa with observation or control treatments now thought to be ineffective in melanoma. Results varied across trials, with some showing improvement in RFS,[365-373] a few showing improvement in OS,[367,369,370,372] but others showing no improvement in RFS or OS or effects with borderline statistical significance.[370,371,374-381] Meta-analyses including data from a large number of trials have shown that improvements in RFS and OS are statistically significant, but small. A recent meta-analysis reported improvements in 5- and 10-year event-free survival and OS of less than 4%.[382]

IFN alfa has been supplanted, however, by targeted therapy and immune checkpoint inhibitor options based on results from recent and ongoing prospective randomized trials.[383-387] Although trials supporting immune checkpoint inhibitor and targeted therapy as adjuvant treatment options did not compare these agents to IFN alfa, the NCCN Melanoma Panel considers these agents to be more effective and better tolerated than IFN alfa, and therefore no longer recommends IFN alfa for adjuvant treatment of cutaneous melanoma.

For several years biochemotherapy was among the listed options for adjuvant treatment of resected high-risk stage III melanoma. Inclusion of biochemotherapy as an adjuvant option was based on results from the SWOG S0008 phase 3 randomized trial showing that the combination of cisplatin, vinblastine, dacarbazine, IL-2, and IFN alfa improved RFS compared with high-dose IFN alfa-2b (median of 4.0 years vs. 1.9 years; HR, 0.75 with 95% CI, 0.58–0.97; P = .03).[388] Although the studies supporting adjuvant immune checkpoint inhibitor and targeted therapy options did not compare these newer approaches with biochemotherapy, the latter has been removed from the list of adjuvant options because it was rarely being used at NCCN Member Institutions due both to its high toxicity profile and to the emergence of more effective adjuvant therapy options.

NCCN Recommendations for Considering Adjuvant Systemic Therapy

Adjuvant treatment outside of a clinical trial is not recommended for patients with stage I/II disease, although the rationale for this recommendation varies across the NCCN Panel. There are no FDA-approved adjuvant immune checkpoint inhibitors or BRAF-targeted therapies for this group of patients. Although most of the trials to date did not include patients with stage I/II disease (Table 5), clinical trials are underway to define the role of adjuvant checkpoint inhibitors in high-risk stage II patients.[389,390]

For patients with resected advanced melanoma, there have been a number of prospective randomized trials suggesting that immune checkpoint inhibitor and BRAF-targeted therapy are effective options for adjuvant treatment. Data from these trials are summarized in Table 5. These trials, the FDA-approved indications (Table 6), and the NCCN recommendations (Table 7) based on these trials are discussed in greater detail in the sections below. Selection of a specific adjuvant systemic therapy for patients with resected advanced melanoma depends on many factors, including risk of recurrence, potential clinical benefit, potential toxicities, patient preference, patient age, and comorbidities. Other options include participation in a clinical trial and observation.

The most important factor to consider is the risk of recurrence and/or death from disease. Stage IIIA is the lowest risk group for which the NCCN

Guidelines recommend considering adjuvant treatment. Several of the recent phase III randomized trials testing immune checkpoint inhibitors or BRAF-targeted therapies have included some stage IIIA patients; generally, the trials have included only those sentinel node-positive patients with a nodal metastasis at least 1 mm in diameter, as these were judged to be higher risk (Table 5). It is important to note, however, that the entry criteria for these trials were based on AJCC 7th Edition staging, and that patients with stage IIIA disease as defined by AJCC 7th Edition staging comprise a higher risk group than stage IIIA as defined by AJCC 8th Edition staging, which also incorporates Breslow thickness into stage III disease (5-year melanoma-specific survival for AJCC 7th Edition stage IIIA is 78%, compared to 93% for AJCC 8th Edition stage IIIA).[391] In patients with resected stage III disease at low risk of recurrence (eg, AJCC 8th Edition stage IIIA and/or those with SLN metastasis <1 mm), the toxicity of adjuvant therapy may outweigh the benefit and should be discussed with the patient.

Across the NCCN Panel, opinions vary regarding the strength of evidence supporting adjuvant systemic therapy (using the currently recommended options shown in Table 7) for resected stage III/IV disease. NCCN Panel Members agree that recommendations for systemic adjuvant treatment (Table 7) are supported by improvements in RFS as reported in recent and ongoing prospective randomized trials (Table 5). Some panel members believe that RFS improvement and available survival data suggest that upfront adjuvant systemic therapy is preferable, and expect that further follow-up will confirm that adjuvant treatment (with the currently recommended agents) improves DSS. Other panel members are less convinced by the available data, and would prefer to wait for longer term follow-up confirming that the observed improvement in RFS translates into improvement in OS/DSS before making a strong case for using upfront adjuvant treatment in most patients with stage III disease. The argument against routine adjuvant therapy for all patients with resected stage III disease is that, unless the observed improvement in RFS translates into a corresponding improvement in OS/DSS, a more selective approach to the use of adjuvant therapy may be prudent, with the idea that forgoing upfront adjuvant therapy and then treating in the event of relapse may result in similar OS/DSS but lower overall risk of toxicity.

When considering whether adjuvant therapy is appropriate for a patient with regional disease limited to clinically occult nodal metastases, it is also important to note that entry criteria for all the trials in Table 5 required complete resection of all disease, including primary tumor excision with adequate margins and CLND in patients with nodal metastases detected by SLNB. However, based on results from two prospective randomized trials (MSLT-II and DeCOG) demonstrating that CLND did not improve DSS or OS in patients with clinically occult nodal disease,[275,392] it is reasonable to consider nodal basin ultrasound surveillance in lieu of CLND. Although it is unclear whether the recommended adjuvant treatment options have similar efficacy in the absence of CLND following a positive SLNB, the NCCN Melanoma Panel thinks that CLND should not be a factor in the decision to use adjuvant therapy in patients whose nodal metastases are detected by SLNB.

Risk of toxicity is the other major consideration when deciding whether a patient with stage III disease should receive adjuvant therapy. Table 5 includes AE rates observed in each of the prospective randomized trials testing immune checkpoint inhibitors and BRAF-targeted therapies in the adjuvant setting. Although anti-PD-1 agents and BRAF/MEK inhibitor therapy are associated with lower rates of toxicity than historical adjuvant therapy options (ie, IFN alfa, biochemotherapy), grade 3–4 AEs (all cause) were observed in 25% to 41% of patients treated in adjuvant trials,[385-387] and a small proportion of patients receiving adjuvant immune checkpoint inhibitors can develop life-long immune-related AEs (irAEs). In patients with prior exposure to anti-PD-1 therapy and for whom adjuvant

ipilimumab is an option, the decision should be informed by careful consideration of a patient's individual risk of recurrence and his/her ability to tolerate and manage toxicities. Patients selected for the adjuvant trials shown in Table 5 all had good performance status (ECOG 0 or 1), and the immunotherapy trials also excluded patients with autoimmune disease or uncontrolled infection, and those requiring systemic glucocorticoids.[384-387] Prior to starting any adjuvant therapy, the NCCN Panel recommends reviewing the U.S. prescribing information for each agent being considered, to ensure that contraindications are identified, and for dosing options and administration and recommendations. For monitoring and management of irAEs associated with immune checkpoint inhibitors, refer to the NCCN Guidelines for Management of Immunotherapy-Related Toxicities.

Table 5. Immune Checkpoint Inhibitor and Targeted Therapy: Randomized Trial Data for Adjuvant Treatment

Trial		Stages Included[a]	Treatment Arms	Median Follow-up	Efficacy Analysis[b]			AEs[c] Any grade Grade 3–4 Grade 5
Name and Reference	Phase Design				RFS or DFS	DMFS	OS	
Immune Checkpoint Inhibitors								
EORTC 18071 NCT00636168 Eggermont 2016[384]	III DB RCT	IIIA >1 mm, IIIB/C no IT	HD-Ipi (n = 475) Pbo (n = 476)	5.3 y	5-y: 41% vs. 30% HR = 0.76 [0.64–0.89] *P* < .001	5-y: 48 vs. 39% HR = 0.76 [0.64–0.92] P = .002	5-y: 65% vs. 54% HR = 0.72 [0.58–0.88] *P* = .001	99% vs. 91% 54% vs. 26% 1.5 vs. 1.3%
CheckMate 238 NCT02388906 Weber 2017[385]	III DB RCT	IIIB/C[d] IV	Nivo + Pbo (n = 453) HD-Ipi + Pbo (n = 453)	1.6 y	1-y: 71% vs. 61%[e] HR = 0.65 [0.51–0.83] *P* < .001	1-y: 80 vs. 73% HR = 0.73 [0.55–0.95]	NR	97% vs. 99% 25% vs. 55% 0 vs. 0.4%
KEYNOTE-054 NCT02362594 Eggermont 2018[386]	III DB RCT	IIIA >1 mm, IIIB/C no IT[f]	Pembro (n = 514) Pbo (n = 505)	1.2 y	1-y: 75% vs. 61% HR = 0.57 [0.43–0.74] *P* < .001	NR[g]	NR	93% vs. 90% 32% vs. 19% 0.2% vs. 0
BRAF-Targeted Therapy								
COMBI-AD NCT01682083 Long 2017[387]	III DB RCT	IIIA >1 mm, IIIB/C[h]	Dab + Tram (n = 438) Pbo (n = 432)	2.8 y	3-y: 58% vs. 39% HR = 0.47 [0.39–0.58] *P* < .001	NR[i] HR = 0.51 [0.40–0.65] Nominal *P* < .001	3-y: 86% vs. 77% HR = 0.57 [0.42–0.79] *P* = .0006[j]	97% vs. 88% 41% vs. 14% 0.2% vs. 0
BRIM8 NCT01667419 Maio 2018[393]	III DB RCT	IIC, IIIA >1 mm, IIIB/C no IT[k]	Vem (n = 250) Pbo (n = 248)	2.5 y, 2.8 y[l]	2-y: 62% vs. 53% HR = 0.65 [0.50–0.85] *P* = .0013	2-y: 72% vs. 65% HR = 0.70 [0.52–0.96] *P* = .027	2-y: 90% vs. 86% HR = 0.76 [0.49–1.18] *P* = .2165	NR 57% vs. 15% 0.4% vs. 0

>1 mm, at least one lymph node with metastasis diameter >1 mm; AEs, adverse events; Dab, dabrafenib; DB, double-blind; DFS, disease-free survival; DMFS, distant metastasis-free survival; HD-ipi, high-dose ipilimumab (10 mg/kg every 3 weeks for 4 doses, then every 3 months for up to 3 years); HR, hazard ratio, with 95% CI in square brackets; IFN, interferon; ipi, ipilimumab; IT, in-transit metastases; Nivo, nivolumab; NR, not reported; OL, open-label; OS, overall survival; Pbo, placebo; Pembro, pembrolizumab; RCT, randomized controlled trial; RFS, recurrence-free survival or relapse-free survival; Tram, trametinib; vem, vemurafenib

[a] Defined per AJCC 7th Edition Staging.

[b] Unless otherwise noted, Kaplan-Meier method was used to determine rates of RFS, DFS, DMFS, and OS. Square brackets show 95% CI for HR.

[c] Percent of patients who experienced ≥1 AE of any grade, grade 3–4, grade 5. Includes all AEs, regardless of causality. Note that AE rates provided in subsequent tables are lower because they are rates of AEs reported as related to study treatment.

[d] Patients with stage IIIB/C were required to have clinically detectable lymph nodes (confirmed by pathology) and/or ulcerated primary lesions. This implies that patients with in-transit disease may have been included, provided that they also had ≥1 clinically detectable nodal metastasis and/or ulceration in the primary lesion. More than 90% of patients with stage III had either microscopic or macroscopic lymph node involvement.

[e] RFS 1.5-y rate: 66% vs. 3% for nivolumab versus ipilimumab.

[f] Although entry criteria excluded patients with in-transit metastases, the analysis included 6 patients with in-transit metastasis and nodal disease.

[g] Distant metastasis occurred in 78 (15.2%) vs. 138 (27.3%) of patients in the pembrolizumab vs. placebo arms. Distant metastases as first type of recurrence, 18-mo rate: 17% vs. 30%, HR, 0.53; 95% 0.37–0.76.

[h] Patients were required to have *BRAF* V600E or V600K mutation. Entry criteria allowed patients presenting with initial resectable lymph node recurrence after a diagnosis of stage I or II melanoma. In-transit metastases were present in 51 patients (12%) in the dab/tram arm and 36 patients (8%) in the placebo arm. Patients were required to have CLND, so it seems unlikely that any patients with intralymphatic disease alone (no nodal metastases) were admitted to the trial.

[l] Patients with distant metastases or death (whole study period), in dabrafenib/trametinib vs. placebo arm: 25% vs. 35%

[j] Despite this low *P* value, the between-group difference was not significant because it did not cross the prespecified conservative interim boundary of *P* = .000019.

[k] Patients were required to have *BRAF* V600 mutation.

[l] Median follow-up for stage IIC-IIIB, stage IIIC.

Specific Systemic Therapy Options for Adjuvant Treatment

A number of prospective randomized trials have shown that immune checkpoint inhibitors and BRAF-targeted therapies are effective for unresectable stage III and stage IV melanoma, [92-95,136,403-413] and these drugs are now FDA approved and widely used in this setting. The FDA-approved indications are summarized in Table 6. Based on their efficacy for unresectable advanced disease, many of these therapies are now the subject of ongoing prospective randomized trials to determine whether they provide clinical benefit as adjuvant treatment for resected advanced disease. Table 5 summarizes published efficacy and safety data from prospective randomized controlled trials testing some of these immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab) and targeted therapies (vemurafenib, dabrafenib/trametinib) for adjuvant treatment of high-risk resected melanoma. Based on data shown in Table 5, some of these therapies have now been approved for adjuvant treatment of resected melanoma (Table 6).

Most of the trials shown in Table 5 excluded patients who had received any kind of prior systemic therapy (ie, EORTC 1807, COMBI-AD, CheckMate 238, KEYNOTE-054, BRIM8).[384-387,393] Each of these trials included a subset stage III disease deemed sufficiently high risk to warrant adjuvant treatment, but the definitions of “high risk” stage III differed across trials. Note that for all these trials AJCC 7th edition staging was used, whereas the NCCN Guidelines have been updated to reflect AJCC 8th edition staging (Table 7). The efficacy and safety data for each of these adjuvant therapies is described in greater detail below.

Table 6. FDA-Approved Indications for Immune Checkpoint Inhibitor and BRAF/MEK Targeted Therapy in Cutaneous Melanoma

Agent	Treatment for Metastatic or Unresectable Disease	Adjuvant Therapy
Immune Checkpoint Inhibitors		
Ipilimumab[394]	Unresectable or metastatic melanoma	Cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
Nivolumab[395]	Unresectable or metastatic melanoma	Melanoma with lymph node involvement or metastatic disease who have undergone complete resection
Pembrolizumab[396]	Unresectable or metastatic melanoma	Melanoma with involvement of lymph node(s) following complete resection
Nivolumab/ipilimumab[394,395]	Unresectable or metastatic melanoma	No FDA approval in this setting
BRAF Targeted Therapies		
Dabrafenib[397]	Unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test	No FDA approval in this setting
Vemurafenib[398]	Unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test	No FDA approval in this setting
BRAF/MEK Combinations		
Dabrafenib/trametinib[397,399]	Unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations as detected by an FDA-approved test	Melanoma with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection
Vemurafenib/cobimetinib[398,400]	Unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test	No FDA approval in this setting
Encorafenib/binimetinib[401,402]	Unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, as detected by an FDA-approved test	No FDA approval in this setting

Immune Checkpoint Inhibitors

Ipilimumab

Ipilimumab, a monoclonal antibody that binds and blocks the function of the immune checkpoint receptor CTLA-4, has been shown to significantly improve progression-free survival (PFS) and OS in patients with unresectable or metastatic melanoma,[403,404] 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 selected patients with completely resected stage III melanoma (Table 5).[383,384] Eligible patients included those with AJCC 7th Edition 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.[383] The trial demonstrated that ipilimumab improved RFS, DMFS, and OS (Table 5). Based on these results the FDA

approved high-dose ipilimumab as adjuvant treatment in melanoma. The FDA-approved indication includes all patient groups included in the trial, patients with stage III in-transit disease (provided they also have at least one nodal metastasis >1 mm diameter), and those who had received prior systemic therapy for melanoma.[383,394]

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.[383,394] In contrast, for treatment of unresectable or metastatic disease, the recommended ipilimumab dose is lower (3 mg/kg) and the treatment duration is shorter (every three weeks for a total of 4 doses).[394] Ipilimumab is associated with a variety of irAEs, and the frequency and severity of these toxicities have been shown to increase with dose.[414-417] A meta-analysis including 1265 patients from 22 clinical trials found that the risk of developing an irAE (high grade) was three-fold higher with ipilimumab 10 mg/kg versus 3 mg/kg.[415]

In EORTC 18071, grade 3–4 AEs were more common with ipilimumab versus placebo (Table 5).[384] Fatal ipilimumab-related AEs occurred in 5 patients (1%), and included colitis (n = 3), myocarditis (n = 1), and multi-organ failure with Guillain-Barré syndrome (n = 1). AEs lead to discontinuation of treatment in 53% of patients who received high-dose adjuvant ipilimumab, compared with 5% of those who received placebo. An ongoing phase III randomized trial (ECOG 1609, NCT01274338) is testing whether adjuvant ipilimumab using the 3 mg/kg dosing will reduce toxicity without reducing clinical benefit. Preliminary results presented at ASCO suggest that RFS may be similar for 3 mg/kg and 10 mg/kg dosing, and that the lower dose may reduce the rate of grade 3–4 AEs.[418] This trial is also comparing adjuvant ipilimumab with adjuvant interferon to determine whether ipilimumab is more effective than the previous standard of care in the adjuvant setting, but data from the IFN alfa arm have not been reported.

Anti-PD-1 Monotherapy

The programmed cell death protein 1 (anti-PD-1) antibodies interfere with ligand binding by the T-cell surface receptor PD-1, resulting in enhanced T-cell activation.[419,420] Two PD-1–directed antibodies, nivolumab and pembrolizumab, have been tested as adjuvant treatment for resected melanoma in two phase III randomized trials (CheckMate 238 and KEYNOTE-054, respectively; Table 5).[385,386]

The CheckMate 238 study compared adjuvant nivolumab to adjuvant ipilimumab (10 mg/kg) in select patients with resected stage IIIB/C or stage IV (Table 5). At a median 19.5 months follow-up, nivolumab was associated with a clinically meaningful and statistically significant improvement in RFS and DMFS. The percent of patients experiencing grade 3–4 AEs was 30% lower in the nivolumab versus ipilimumab arm.[385] Further follow-up is needed to determine whether nivolumab favorably impacts OS compared to ipilimumab. Subgroup analyses also suggest that nivolumab significantly improves RFS (relative to ipilimumab) regardless of *BRAF* mutation status or PD-L1 expression status. Based on the demonstrated improvement in RFS, the FDA approved nivolumab for adjuvant treatment of resected nodal or metastatic melanoma (Table 6). Although the trial entry criteria required patients with stage IIIB/C disease (AJCC 7th Edition) to have clinically detected lymph nodes and/or ulcerated primary, the FDA-approved indication is broader, including all patients with “lymph node involvement.”

In the KEYNOTE-054 trial, pembrolizumab was compared with placebo in selected patients with resected stage III melanoma (Tables 1). At a median follow-up of 1.2 years, pembrolizumab improved RFS and reduced risk of distant metastases; OS data were not mature at the time of the initial report.[386] Although the fraction of patients who experienced any

grade of AE was similar across arms, high-grade AEs were somewhat more common in the pembrolizumab arm. Subgroup analyses suggest that improvement in RFS with pembrolizumab (relative to placebo) is not related to PD-L1 expression or *BRAF* mutation status.

Although there are no data from prospective randomized trials directly comparing adjuvant nivolumab versus pembrolizumab, the results from CheckMate 238 and KEYNOTE-054 suggest that these agents have similar efficacy and safety in the adjuvant setting.[385,386]

NCCN Recommendations for Adjuvant Immune Checkpoint Inhibitors

A summary of the NCCN-recommended adjuvant systemic immune checkpoint inhibitor options and category of evidence and consensus for each of these recommendations are listed in Table 7 according to clinical/pathologic stage and primary treatment. Based on the results from CheckMate 238, the NCCN Melanoma Panel agrees that nivolumab should be listed as an adjuvant postoperative treatment option for patients with stage III-IV at presentation, as well as for patients with recurrent stage III/IV disease. Whereas the NCCN Panel considers adjuvant nivolumab to be a reasonable option across a wider range of patients than were included in the CheckMate 238 trial, nivolumab is a category 1 option only in specific subgroups, based on the makeup of the study population and strength of data for specific subgroups. The NCCN Panel agreed that results from CheckMate 238 provide high-level evidence that postoperative adjuvant nivolumab provides RFS benefit to patients who present or recur with clinically node positive disease (Table 7). Because the trial excluded patients with stage IIIA disease (AJCC 7th Edition staging), the panel is less confident about the benefit of adjuvant nivolumab in patients whose nodal disease is detected by SLNB. The recommendation for adjuvant nivolumab is category 1 only for stage IIIB/C with lymph node metastases (AJCC 7th Edition), used as selection criteria in the trial. Note that definitions of the stage III substages were significantly revised in the AJCC 8th Edition update, such that some cases that were stage IIIB/C per the AJCC 7th Edition would be reclassified as stage IIIA per the AJCC 8th Edition, and vice versa. In addition, some cases that were stage IIIC per the AJCC 7th Edition would be reclassified as stage IIID per the AJCC 8th Edition. Results of trials based on AJCC 7th Edition staging cannot be directly mapped to patients staged using the AJCC 8th Edition, and all decisions should be informed by a thorough understanding of the probability of recurrence and the risks and potential benefits of a given adjuvant therapy. Although there may have been some patients with (resectable) in-transit disease in this trial, data from these patients were not reported separately, so adjuvant nivolumab is a category 2A recommendation in patients with satellite/in-transit disease (at initial presentation or recurrence), if complete excision to clear margins is achieved. The NCCN Panel recommends referring to the FDA label for nivolumab for details on dosing and treatment administration.[395]

Based on the results of the KEYNOTE-054 trial, the NCCN Panel recommends pembrolizumab as an adjuvant therapy option for patients with stage III disease (at presentation or recurrence) (Table 7). Similar to the situation with nivolumab, the NCCN Panel considers adjuvant pembrolizumab to be a reasonable option across a wider range of stage III patients than were included in the KEYNOTE-054, but it is a category 1 option only in specific subgroups (Table 7). The NCCN Panel agreed that the results from KEYNOTE-054 support adjuvant pembrolizumab as a category 1 option for patients with clinically detected nodal metastases. For patients with clinically occult nodal disease, the category 1 recommendation is limited to the subgroup of patients included in the trial: stage IIIA with at least one nodal metastasis >1 mm or stage IIIB/C, per AJCC 7th Edition staging definitions. Patients with in-transit metastases were excluded from this trial, so adjuvant pembrolizumab is a category 2A option in this setting.

Although patients with stage IV disease were not included in the KEYNOTE-054 trial, the NCCN Panel included adjuvant pembrolizumab as a category 2A option for resected stage IV disease. Because all the prospective randomized trial data thus far—both in the adjuvant setting and in the treatment of unresectable or distant metastatic melanoma—indicate that pembrolizumab and nivolumab are very similar in terms of efficacy and safety, the NCCN Panel voted to recommend pembrolizumab in all the adjuvant settings where nivolumab was recommended (Table 7).

Although results from EORTC 18071 showed that adjuvant high-dose ipilimumab improved RFS, DMFS, and OS compared with placebo, results from CheckMate 238 showed that adjuvant nivolumab improved RFS compared to high-dose ipilimumab with a better safety profile (Table 5). Although, in contrast to adjuvant high-dose ipilimumab, the impact of adjuvant anti-PD-1 therapy on OS is not yet reported, the panel considered the relative difference in toxicity to be more important in the adjuvant setting. Moreover, as prospective randomized trials have shown anti-PD-1 therapy to be associated with better OS compared with ipilimumab in patients with unresectable/distant metastatic disease,[421,422] it is reasonable to extrapolate this observation into the adjuvant setting. Although not all the trials supporting anti-PD-1 therapy and BRAF-targeted therapy as adjuvant treatment options compared these agents to ipilimumab, the NCCN Melanoma Panel considers these agents to be more effective and better tolerated than ipilimumab, and therefore no longer recommends ipilimumab for adjuvant treatment (following resection) for patients with stage III disease at presentation. Ipilimumab is *no longer* listed among the options for first-line adjuvant systemic therapy for stage III disease shown on ME-4, ME-5, and ME-7 (Table 7).

For patients with a nodal recurrence after previous exposure to an anti-PD-1 agent, repeat exposure to adjuvant nivolumab or pembrolizumab may be less effective. This is a clinical scenario where ipilimumab remains an adjuvant treatment option (Table 7, ME-14/15). Based on similar logic, the NCCN Panel voted to include adjuvant ipilimumab as an option for patients with resected stage IV disease who have prior exposure to anti-PD-1 agents (See Table 7 and ME-16 in the algorithm). The preferred ipilimumab dose in the adjuvant setting varies across NCCN Member Institutions because, although the efficacy of ipilimumab for adjuvant treatment was demonstrated in EORTC 18071 using the high dose (10 mg/kg), the lower dose (3 mg/kg) is safer, and preliminary ECOG 1609 data presented at ASCO 2017 suggest that the lower dose may be equally effective in the adjuvant setting.[418] At present, this adjuvant ipilimumab dose reduction represents what the panel felt was a prudent but not yet evidence-based extrapolation of data derived from trials of its use in other settings.

BRAF-Targeted Therapy

BRAF-targeted therapy has been tested as adjuvant treatment for resected melanoma in two prospective, double-blind, randomized controlled trials, COMBI-AD and BRIM8 (Table 5).[387,393] COMBI-AD showed that in select patients with resected stage III disease and *BRAF* V600 E/K mutation, adjuvant treatment with the BRAF/MEK inhibitor combination dabrafenib/trametinib improved RFS and reduced risk of distant metastasis, albeit with a higher risk of toxicity (as expected).[387] OS rate was higher with dabrafenib/trametinib versus placebo, but the P value (P = .0006) did not meet the prespecified interim boundary (Table 5). The trial included patients with resected AJCC 7th Edition stage IIIA who had at least one lymph node metastasis >1 mm, stage IIIB, or stage IIIC. Subgroup analyses showed RFS was significantly better with dabrafenib/trametinib for patients with *BRAF* V600E, and likely also improves RFS for patients with the less common *BRAF* V600K mutation. Based on results from COMBI-AD, dabrafenib/trametinib combination therapy was FDA approved as adjuvant therapy for patients with *BRAF* V600E/K mutations. Whereas COMBI-AD entry criteria required patients

with stage IIIA (AJCC 7th Edition) to have at least one lymph node metastasis >1 mm, the FDA-approved indication was broader, including all patients with lymph node involvement and complete resection (Table 6).

BRIM8 showed that in select patients with resected AJCC 7th Edition stage IIC-III disease and *BRAF* V600 mutation, adjuvant treatment with the BRAF inhibitor vemurafenib monotherapy improved DFS and possibly DMFS compared with placebo (Table 5).[393] The effect on OS was not statistically significant, but these data remain immature. Patients with stage III disease in this trial were restricted to those who had AJCC 7th Edition stage IIIA with at least one node with diameter >1 mm, or stage IIIB/C without in-transit metastases (Table 5). As expected, BRIM8 results showed that adjuvant vemurafenib was associated with higher rates of toxicity than placebo.[393] Consistent with results from prospective randomized trials comparing BRAF/MEK inhibitor combination therapy with BRAF inhibitor monotherapy for the treatment of unresectable or distant metastatic disease,[411-413] safety results from BRIM8 showed that adjuvant vemurafenib was associated with an increase in hyperproliferative cutaneous AEs (16% vs. 2% for vemurafenib vs. placebo).[393] This increase was not seen for dabrafenib/trametinib (vs. placebo) in the COMBI-AD trial.[387] Given the improved efficacy/safety profile of BRAF/MEK inhibitor combination therapy compared to BRAF inhibitor monotherapy,[411-413] vemurafenib monotherapy is not FDA approved for adjuvant treatment of melanoma (Table 6).

NCCN Recommendations for BRAF-Targeted Adjuvant Therapy

Based on the results from the COMBI-AD trial, adjuvant dabrafenib/trametinib combination therapy is a recommended option for patients with resected stage III or recurrent disease and who harbor a *BRAF* V600-activating mutation (Table 7). Dabrafenib/trametinib is an adjuvant treatment option for all patients with stage III disease, even those categories of patients that were not included in the trial. The NCCN Panel agreed that the data from the COMBI-AD trial provide high-level evidence that adjuvant dabrafenib/trametinib provide clinical benefit in patients with nodal metastases clinically detected at initial presentation or recurrence (following complete resection and CLND). However, among patients whose regional disease consists solely of clinically occult nodal metastases, the NCCN category 1 recommendation is limited to those whose extent of disease matches study entry criteria: stage IIIA with at least one nodal metastasis >1 mm or stage IIIB/C, as defined by AJCC 7th Edition staging. Although COMBI-AD did include patients with in-transit metastases, results from these patients were not reported separately, so the adjuvant dabrafenib/trametinib is a category 2A option for patients with satellite/in-transit disease (if completely excised to clear margins). As the COMBI-AD trial excluded patients with distant metastases, dabrafenib/trametinib is not a recommended adjuvant treatment option for resected stage IV disease.

Although BRIM8 showed that adjuvant vemurafenib improved RFS and lowered risk of distant metastases relative to placebo, vemurafenib is not an FDA-approved adjuvant treatment option, and is not recommended by the NCCN Panel. The risk of hyperproliferative cutaneous AEs is considered to outweigh any clinical benefit, especially in the adjuvant setting. Moreover, because trials in patients with unresectable or distant metastatic disease (and *BRAF* V600 mutations) showed that BRAF/MEK inhibitor combination therapies are equally or more effective than BRAF inhibitor monotherapy and have a better safety profile (lower risk of hyperproliferative cutaneous AEs), and because COMBI-AD showed that BRAF/MEK inhibitor combination therapy improves RFS and DMFS in the adjuvant setting (relative to placebo), dabrafenib/trametinib combination therapy is currently the BRAF-targeted adjuvant treatment of choice in melanoma.

Table 7: NCCN Recommended Adjuvant Systemic Therapies

Algorithm Page(s)	Clinical/Pathologic Stage[a]	Primary Treatment	Recommended Options,[b] Category of Evidence and Consensus				
			Obs	Ipi	Nivo	Pembro	Dab/tram[c]
ME-4	Stage III (SLN+)	WLE and SLNB, followed by CLND or nodal ultrasound surveillance	2A	NR	1/2A[d]	1/2A[e]	1/2A[e]
ME-5	Stage III (cN+)	WLE and CLND	2A	NR	1	1	1
ME-6/7	Stage III (clinical or microscopic satellite/ in-transit)	Complete surgical excision to clear margins	2A	NR	2A	2A	2A
ME-8/16	Stage IV resectable	Completely resected	2A	NR/2A[f]	1	2A	NR
ME-12/13	Local satellite/in-transit recurrence	Complete surgical excision to clear margins	2A	NR	2A	2A	2A
ME-14/15	Nodal recurrence	Excise nodal metastasis and CLND (if incomplete/no prior CLND)	2A	NR/1[f]	1	1	1

NR, not recommended; cN+, clinically positive nodes (no in-transit or satellite metastases); CLND, complete lymph node dissection; dab/tram, combination dabrafenib/trametinib; ipi, high-dose ipilimumab (10 mg/kg); nivo, nivolumab; NR, not recommended; Obs, observation; pembro, pembrolizumab; SLN+, regional disease is limited to clinically occult nodal metastases; SLNB, sentinel lymph node biopsy; WLE, wide local excision of primary lesion.

[a] Clinical/Pathologic Stage as described in the NCCN Guideline algorithm. Stages are defined according to AJCC 8th Edition Staging definitions. All nodal metastases must be pathologically confirmed. Initial presentation with stage IV disease or clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated.

[b] Treatment within the context of a clinical trial is always a recommended option.

[c] Dabrafenib/trametinib is recommended only in patients with a *BRAF* V600-activating mutation.

[d] Category 1 for patients with AJCC 7th Edition stage IIIB/C disease.

[e] Category 1 for patients with AJCC 7th Edition stage IIIA with SLN metastasis >1 mm or stage IIIB/C disease.

[f] Ipilimumab recommended only if patient has prior exposure to anti-PD-1 therapy.

Neoadjuvant Systemic Therapy

Data from pilot studies and phase I/II trials have shown promising results for use of BRAF-targeted therapies and immune checkpoint inhibitors as neoadjuvant treatment for resectable stage III-IV melanoma.[423-428] There are a number of ongoing trials testing neoadjuvant therapies for melanoma.[429-443]

NCCN Recommendations for Neoadjuvant Systemic Therapy

Currently there are insufficient data to recommend any specific agent as neoadjuvant therapy for melanoma, but given the promising results in initial trials and the number of trials currently available, the NCCN Panel recommends considering enrollment into a clinical trial of neoadjuvant systemic therapy in patients with borderline resectable lymphadenopathy or for those at very high risk of recurrence after lymphadenectomy.

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.[444]

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 8.

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.[445-448] 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.[449] 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.[450] 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 8).[451] 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 (ORR; 26.4% vs. 5.7%, $P < .001$; complete response in 11% vs. <1%).[450]

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.[450] 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 8). 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.[452] 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.[452-454] 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.[452,453,455]

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[456]).

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 8).[457-459] Although initial response rates are high for injected lesions, intralesional BCG is associated with a number of significant local and occasional systemic adverse effects.[458-460] 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).[461,462] It has similar activity to other intralesional agents, but is not currently available outside of the clinical trial setting (NCT02288897).

Table 8. Intralesional Injection

Injection Agent	Key Published Clinical Studies	Response Rates	
		Injected Lesions	Uninjected Lesions
Talimogene laherparepvec (T-VEC)	• Phase III trial[450,451]	≥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[452,453] and retrospective/observational analyses[463-466] • 2014 systematic reviews and meta-analysis[454]	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[459]	CR: •90% for dermal •45% for subcutaneous	Occasional responses observed
Rose Bengal	• Phase I trial[461] • Phase II trial[462]	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,[458] Morton et al. 1974,[467] and Table 5 in Tan et al. 1993,[457] 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).[468-474] Ablation can be effectively achieved with minimal toxicity,[468,470,471,474] 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.[475-479] 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.[477,480-486]

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.[487-494] One retrospective study included 50 patients with in-transit cutaneously metastatic melanoma treated for at least one month with DPCP.[495] 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,[496-501] but also associated with increased toxicity.[502,503] 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.[504,505] 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.[505-508] 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 ORR of 90% (range 64%–100%) and a median complete response rate of 58% (range, 25%–89%).[507] 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.[507] 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.[509] 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.[510] 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,[511] amenable to repeated applications,[512] and safe for use in elderly patients.[513] Melphalan is commonly used for ILI, often with actinomycin D.[514] Addition of papaverine for cutaneous vasodilation has been shown to increase response rate but also the risk of regional toxicity.[515,516] 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.[515,517-521] An analysis of seven studies, including 576 patients, primarily with stage III disease, treated with melphalan/actinomycin D combination via ILI, showed an ORR of 73%, with complete response in 33% (range, 26%–44% across studies), partial response in 40% (33%–53%), and stable disease in 14%.[514] A smaller pooled analysis of two additional studies (N = 58), one a non-comparative phase II study (NCT00004250), showed similar ORRs for stage IIIB versus stage IIIC disease (48% vs. 40%), and similar 5-year survival rates (38% vs. 52%).[522] 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 ORR 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 Unresectable Stage III or 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.[93,406-413,421,422,450,523-531] Second and emerging third generations of effective agents and combination regimens are now available for treatment of advanced unresectable or metastatic melanoma.

Immune Checkpoint Inhibitors

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.[532-534] 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.[532-534] 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—often 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 signaling cascade that inhibits T-cell activation, limiting the immune response.[535-538] 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.[419,420,539] The importance of this science has recently been recognized by the awarding of the 2018 Nobel Prize in Medicine to James Allison and Tasuku Honjo for their research on CTLA-4 and PD-1.

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 9). 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.[403,404] 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),[540] consistent with findings from phase II trials.[541,542,543] Safety results from these trials showed that ipilimumab is associated with a substantial risk of irAEs, including grade 3–4 events (Table 9) and drug-related deaths (7 in CA184-002).[403] Even higher rates of grade 3–4 irAEs were observed in patients treated with ipilimumab in CA184-024 (Table 9), possibly due to the high dose used (10 mg/kg), or due to combination therapy with dacarbazine, or both.[404] 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.[394] Results from CA184-169, a phase III randomized double-blind trial comparing ipilimumab 10 mg/kg dosing with 3 mg/kg, showed that the higher dose improved OS but was also associated with dramatically higher rates of treatment-related AEs (Table 9).[544] Immune-related AEs associated with ipilimumab and other immune

checkpoint inhibitor regimens are detailed in the *Toxicity of Immune Checkpoint Inhibitors* section.

Given that treatment options may be limited for heavily pretreated patients who have progressed after immune 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 (complete response, partial response, or stable disease) was achieved upon ipilimumab reinduction in most of these patients (20/31).[403,545] 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.[545]

Table 9. Ipilimumab Trials in Advanced Melanoma[a]

Trial			Patients			Efficacy Results[b]			
Name and References	Phase Design	Median Follow-up (months)	Tx Naive	CNS Mets	Treatment Arms	Response Rate	PFS Median (months)	OS Median (months)	Grade 3-4 irAEs[c]
CA184-002 NCT00094653[403]	III RDB	21.0 27.8 17.2	0%[d]	12%[e]	Ipi + gp100 (n = 403) Ipi (n = 137) gp100 (n = 136)	6% *P* = .04 11% *P* = .001 2%	2.8 *P* < .05[f] 2.9 *P* < .001[f] 2.8	10.0 *P* < .001 10.1 *P* = .003 6.4	} 10%–15% 3%
CA184-024 NCT00324155[404,540]	III RDB	Min 36.6	100%	None	DTIC + ipi (n = 250) DTIC + pbo (n = 252)	15% *P* = .09 10%	ND[g] *P* = .0006[f] ND[g]	11.2 *P* < .001 9.1	38% 4%
CA184-169 NCT01515189[544]	III RDB	14.5 11.2	44%[d] 43%[d]	18%[e] 17%[e]	HD-ipi (n = 365) Ipi (n = 362)	15% 12%	2.8 *P* = .16 2.8	15.7 *P* = .04 11.5	30% 14%

CNS Mets, percent of patients with central nervous system metastases at baseline; DTIC, dacarbazine; gp100, gp100 peptide vaccine; HD-ipi, high-dose ipilimumab (10 mg/kg Q3W); ipi, standard dose ipilimumab (3 mg/kg Q3W); irAEs, immune-related adverse events; OL, open-label; pbo, placebo; R, randomized; RDB, randomized, double-blind; Response Rate, percent of patients with complete or partial response as their best overall response; Tx Naive, percent of patients with no prior treatment for unresectable or metastatic disease.

[a] Unresectable stage III or stage IV melanoma.

[b] Median PFS, OS, and P value are based on Kaplan-Meier analysis. P values are for comparisons with the control arm.

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

[d] In CA184-002, all patients had previous treatment with chemotherapy or IL-2, but prior treatment with anti-CTLA-4 or cancer vaccine was not allowed. In CA184-169, previous systemic therapy was allowed, but patients previously treated with BRAF inhibitors or checkpoint inhibitors were excluded.

[e] Patients with active CNS metastases were excluded from the trial.

[f] Although median PFS was similar across arms, P values are based on analyses of the entire Kaplan-Meier curves, which separated at later time points.

[g] In CA184-024, the true median PFS occurred before the first assessment of progression (at week 12).

Anti-PD-1 Agents

While anti-CTLA-4 therapy appears to interfere primarily with the feedback mechanism at the interface between T cells and antigen-presenting dendritic cells, anti-PD-1 inhibitors are thought to interfere primarily with the feedback mechanism at the interface of T cells and tumor cells.[546]

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) (Table 10).[406,407,422,529] Keynote-002 compared pembrolizumab with investigators choice of chemotherapy in patients with unresectable stage III or stage IV melanoma who had previously progressed on ipilimumab, and if *BRAF* V600-mutation positive, also progressed on a BRAF inhibitor.[406] Over 70% of patients in this trial had received two or more prior systemic therapies. Long-term follow-up (median 28 months) in the Keynote-002 trial showed that compared with chemotherapy, pembrolizumab provided higher rates and durations of response, and was associated with long-lasting improvements in PFS (Table 10).[529] The trend toward improved OS was not statistically significant, however, even after adjustment for crossover.[529] Both the poor OS (compared with later trials testing pembrolizumab, see Table 10) and the failure to significantly improve OS compared with chemotherapy may be partly explained by the fact that patients in Keynote-002 were heavily pretreated.[406,529] Keynote-002 results showed that the rates of treatment-related AEs were somewhat lower with pembrolizumab compared with chemotherapy, although the only fatal treatment-related AE occurred in a patient treated with pembrolizumab, and immune-related AEs were of course largely limited to the pembrolizumab arms.[529] Compliance, global health status, and health-related quality of life were better with pembrolizumab compared with chemotherapy.[547]

Results from KEYNOTE-006 showed that in patients with one or fewer prior systemic therapies for advanced disease (and no prior immune checkpoint inhibitors), pembrolizumab improved response rate, PFS, and OS compared with ipilimumab (Table 10).[407,422] Long-term follow-up showed that whereas both pembrolizumab and ipilimumab provided extremely long-lived responses, pembrolizumab provided long-term improvement in PFS and OS compared with ipilimumab monotherapy (Table 10).[422,548] Post-hoc sub-analyses after long-term follow-up (median of 33.9 months) showed that compared with ipilimumab, pembrolizumab was associated with improvement in long-term PFS and OS for both patients who had received one prior systemic therapy and for those previously untreated.[549]

Although initial reports of KEYNOTE-006 showed lower rates of treatment-related toxicities with pembrolizumab compared with ipilimumab, after long-term follow-up the cumulative rates of treatment-related toxicities were similar across treatment arms.[407,422] Toxicity rates were higher with ipilimumab during the first 12 weeks of study treatment, but the frequency of new AEs tapered off after the completion of the ipilimumab regimen (which consisted of a maximum of 4 cycles) around 12 weeks.[422] Although the rate of new AEs was lower with pembrolizumab during the first 12 weeks of study, new AEs continued to develop in the pembrolizumab arm throughout the study period (beyond 12 weeks) as patients continued to receive active treatment (no pre-specified maximum treatment duration).[422]

Results of KEYNOTE-006 support the recommendation that pembrolizumab should be considered as first-line therapy in patients with unresectable or distant metastatic disease.

Kinetics of Response to Pembrolizumab

In clinical trials the median time to response for pembrolizumab of approximately 3 months reflects time of the first tumor response assessment (12 weeks), similar to ipilimumab and nivolumab, and similar

to chemotherapy.[406,407,550,551] Long-term follow-up from several studies has shown that late responses to pembrolizumab can be observed more than a year after the start of treatment, and that initial partial responses may become complete responses with time.[406,407,529,549,551] A pooled analysis of cohorts from KEYNOTE-001 with long-term follow-up (median 43 months) showed that 16% of patients achieved complete response, with median time to complete response of 12 months, ranging from 3 to 36 months.[551]

Across trials long-term follow-up has shown that responses to pembrolizumab are very long-lived, with median duration ranging from 23 months (2 mg/kg Q3W arm in Keynote-002) to much longer (eg, not reached even after 33.9 months follow-up in KEYNOTE-006).[405,529,549,551] In contrast, median duration of response was 6.8 months for patients treated with chemotherapy in the KEYNOTE-002 trial.[529] Pooled analysis of Keynote-001 cohorts with long-term follow-up (median 43 months) showed that although complete responses to pembrolizumab took some time to develop, they were highly durable (88% of complete responses persisting after a median follow-up time of 30 months from the first declaration of complete response; 91% DFS 24 months after complete response), even among patients who discontinued pembrolizumab.[551]

Table 10. Pembrolizumab Trials in Advanced Melanoma[a]

Trial			Patients			Efficacy Results[c]			Grade 3–4 Tx-Related AEs[d]
Name and References	Phase Design	Median Follow-up (months)	Tx Naive	Brain Mets[b]	Treatment Arms	Response Rate	PFS 2-year Rate	OS 2-year Rate	
KEYNOTE-002 NCT01704287[406,529]	II R, OL	28	None[e]	--	Pembro 2 mg/kg Q3W (n = 180)	22% $P < .0001$[f]	16% $P < .0001$	36% $P = .117$[f]	14%
					Pembro 10 mg/kg Q3W (n = 181)	28% $P < .0001$	22% $P < .0001$	38% $P = .011$	16%[g]
					Chemo (n = 179)	4%	<1%	30%	26%
KEYNOTE-006 NCT01866319[407,422]	III R, OL	22.9	34%[h]	9%	Pembro 10 mg/kg Q2W (n = 279)	37% $P < .001$[i]	31% $P < .0001$[i]	55% $P = .0009$[i]	17%
					Pembro 10 mg/kg Q3W (n = 277)	36% $P < .001$	28% $P < .0001$	55% $P = .0008$	17%
					Ipi 3 mg/kg Q3W x 4 doses (n = 278)	13%	14%	43%	20%

--, data not reported; AEs, adverse events; Chemo, Investigator's choice chemotherapy; Brain Mets, percent of patients with central nervous system metastases at baseline; ipi, ipilimumab; OL, open label; pembro, pembrolizumab; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomized; Tx Naive, percent of patients with no prior treatment for unresectable or metastatic disease; Tx, treatment.

[a] Unresectable stage III or stage IV melanoma.

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

[c] P values are for comparisons with the control arm. PFS and OS 2-year rates are based on the Kaplan-Meier method.

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

[e] In KEYNOTE-002, all patients were previously treated with ipilimumab and progressed; patients with *BRAF* mutations were also previously treated with BRAF or MEK inhibitors, or both.

[f] In KEYNOTE-002, comparison of pembrolizumab 2 mg/kg vs. 10 mg/kg arms showed no difference in overall response rate ($P = .214$) or OS ($P = .290$).

[g] In KEYNOTE-002, there was 1 fatal treatment-related AE in the pembrolizumab 10 mg/kg arm.

[h] In KEYNOTE-006, patients could have had up to one prior systemic therapy, but patients previously treated with checkpoint inhibitors were excluded.

[i] In KEYNOTE-006, comparison of the pembrolizumab Q2W and Q3W arms showed no difference in overall response rate ($P = .82$), PFS ($P = .62$), or OS ($P = .93$).

Nivolumab

Checkmate 037 compared nivolumab versus investigator's choice chemotherapy in patients with unresectable stage III or stage IV melanoma who had previously progressed on ipilimumab, and if *BRAF* V600-mutation positive, also progressed on a BRAF inhibitor.[523] Over 70% of patients in this trial had received two or more prior systemic therapies. Results from Checkmate 037 show that nivolumab improved response rate and duration compared with chemotherapy (Table 11). However, after approximately 2 years of follow-up, the improvement in response did not translate into improved PFS or OS (Table 11).[410,523] Safety results suggest that nivolumab may be better tolerated than chemotherapy in heavily pretreated patients with advanced disease (Table 11).[410,523]

Two subsequent phase III clinical trials in previously untreated patients have demonstrated nivolumab efficacy in unresectable stage III or stage IV melanoma (Table 11). As expected, the response rates to nivolumab in previously untreated patients in Checkmate 066 and 067 were higher than those seen in patients with prior systemic therapy for advanced disease treated in Checkmate 037 (Table 11). Results from Checkmate 066 showed that nivolumab improved response rate, PFS, and OS compared with chemotherapy.[526,530] The percent of grade 3–4 treatment-related AEs was initially lower with nivolumab compared to chemotherapy (12% vs. 18%),[526] but longer follow-up showed that treatment-related AEs continued to develop in the nivolumab arm, diminishing the difference between the two arms (Table 11).[530] It is important to point out, however, that due to shorter time to progression, patients in the chemotherapy arm had shorter treatment duration than those in the nivolumab arm. Remarkably, the survival curve suggests that nivolumab may lead to long-term survival in up to 40% of patients.[530] Results from Checkmate 067 showed that nivolumab (monotherapy) improved response rate, PFS, and OS compared with ipilimumab (monotherapy) (Table 11).[408,421,531] Although initial reports showed lower toxicity with nivolumab compared with ipilimumab (grade 3–4 treatment-related AEs for nivolumab vs. ipilimumab: 16% vs. 27%),[408] longer follow-up showed that treatment-related AEs continued to develop in the nivolumab arm, reducing the difference between arms (Table 11).[531] Analysis of Checkmate 067 results also showed that PFS and OS were similar for patients who discontinued nivolumab due to toxicity and patients who continued treatment.[531]

The results of Checkmate 066 and 067 supported the recommendation that nivolumab should be considered as first-line therapy in patients with unresectable or metastatic disease.

Kinetics of Response to Nivolumab

Across trials the apparent median time to response for nivolumab closely reflects the time of the first response assessment (9 or 12 weeks),[408,410,523,526,528] similar to chemotherapy, ipilimumab, and pembrolizumab.[403,406,407] Initial analyses of Checkmate 037, 066, and 067 showed lower rates of complete response than were reported in the final analyses after longer follow-up.[408,410,421,523,526,530,531] Similar to pembrolizumab, late complete responses to nivolumab can be seen more than a year after the start of treatment. Across trials responses to nivolumab tend to be very long-lived, with median duration ranging from 31.9 months (Checkmate 037) to much longer (eg, not reached even after 38.4 months minimum follow-up in Checkmate 066).[409,410,421,530,531] In contrast, duration of response was much shorter in chemotherapy control arms (median 12.8 months in CheckMate 037, median 6.0 months in Checkmate 066).[410,530] Across trials, responses to nivolumab tend to persist after discontinuation of treatment.[409,410,523,528,530]

Table 11. Nivolumab Trials in Advanced Melanoma[a]

Trial			Patients			Efficacy Results[c]						Grade 3–4 Tx-Related AEs[d]
Name and References	Phase Design	Median Follow-up (months)	Tx Naive	CNS Mets[b]	Treatment Arms	Response Rate		Median PFS (months)		Median OS (months)		
CheckMate 037 NCT01721746[410,523]	III R, OL	~24	0[e]	20%	Nivo (n = 272)	27%		3.1	NS[f]	15.7	*P* = .716	14%
				14%	Chemo (n = 133)	10%		3.7		14.4		34%
CheckMate 066 NCT01721772[526,530]	III RDB	38[g]	100%	3.6%	Nivo (n = 210)	43%	*P* < .001	5.1	*P* < .001	37.5	*P* < .001	15%
		39[g]			DTIC (n = 208)	14%		2.2		11.2		18%
CheckMate 067 NCT01844505[408,421,531]	III RDB	47	100%	3.6%	Nivo/ipi, then nivo (n = 314)	58%	*P* < .0001[h]	11.5	*P* < .0001[h]	NR	*P* < .0001[h]	59%
		36			Nivo (n = 316)	45%	*P* < .0001	6.9	*P* < .0001	36.9	*P* < .0001	22%
		19			Ipi (n = 315)	19%		2.9		19.9		28%
CheckMate 069 NCT01927419[409,528]	II RDB	25	100%	3%[g]	Nivo/ipi, then nivo (n = 95)	59%	*P* < .0001	NR	*P* < .0001	NR	*P* = .26	54%
					Ipi (n = 47)	11%		3.0		NR		20%

Chemo, Investigator's choice chemotherapy of single-agent dacarbazine or carboplatin/paclitaxel combination; CNS Mets, percent of patients with central nervous system metastases at baseline; DTIC, dacarbazine; ipi, ipilimumab; nivo, nivolumab; NR, not reached (longer follow-up needed); NS, not statistically significant; OL, open-label; R, randomized; RDB, randomized, double blind; Tx Naïve, percent of patients with no prior treatment for unresectable or distant metastatic disease.

[a] Unresectable stage III or stage IV melanoma.

[b] Patients with active CNS metastases were excluded from the trials. For all studies except Checkmate 067, the percentage of patients with a history of brain metastases is shown. For Checkmate 067 the percentage of patient with brain metastases at baseline is shown.

[c] Response rate is the percentage of patients that achieved complete or partial response. P values are for comparisons with the control arm. Median PFS and OS were determined using the Kaplan-Meier method.

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

[e] Entry criteria for the Checkmate 037 trial stipulated that patients must have progressed on ipilimumab, and if *BRAF*-V600 mutation positive, also progressed on a BRAF inhibitor.

[f] In the Checkmate 037 trial, PFS was not significantly different between arms (HR, 1.03; 95% CI, 0.78–1.436).

[g] Median follow-up for Checkmate 066 was not reported, but minimum follow-up was 39 months in each arm.

[h] In Checkmate 067, objective response rates were higher with nivolumab/ipilimumab combination versus nivolumab monotherapy: 58% (95% CI, 52.6–63.8) vs. 45% (95% CI, 39.1–50.3). Descriptive analysis suggests that nivolumab/ipilimumab combination therapy improves PFS compared with single-agent nivolumab (HR, 0.79; 95% CI, 0.65–0.97), but the trend toward improved OS did not reach statistical significance (HR, 0.84; 95% CI, 0.67–1.05).

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

CTLA-4 and PD-1 inhibitor combination therapies have been investigated in a number of trials in unresectable stage III or stage IV melanoma (eg, CA209-004, Checkmate 064, Checkmate 067, Checkmate 069, Checkmate 204, NCT02731729, NCT02374242, Keynote-029).[408,528,552-558] Results from two randomized trials (Checkmate 067 and Checkmate 069)

demonstrated that the response rate with ipilimumab/nivolumab combination therapy was substantially higher than with ipilimumab alone (Table 11).[408,409,421,528,531] Both trials showed that PFS was substantially better with combination therapy compared with ipilimumab monotherapy (Table 11).[408,421,531] Checkmate 067 showed that OS was improved with combination therapy versus ipilimumab (Table 11), and these effects persisted through long-term follow-up. The 4-year survival rates in Checkmate 067 are 53% for ipilimumab/nivolumab, 46% for single-agent nivolumab, and 30% for single-agent ipilimumab.[531] In Checkmate 069, a smaller randomized phase II study, results after 25 months median follow-up showed a trend toward improved OS with combination therapy compared with ipilimumab (2-year rate: 63.8% [95% CI, 53.3–72.6] vs. 53.6% [38.1–66.8] that was not statistically significant, although at the time of analysis median OS had not been reached in either arm (Table 11).[409,528]

Checkmate 067 included an arm of patients treated with nivolumab monotherapy, although it was not powered to compare results to patients treated with combination therapy.[408] Response rate was higher with nivolumab/ipilimumab combination therapy compared with nivolumab monotherapy (58% vs. 45%), and descriptive analysis showed improved PFS (HR, 0.79; 95% CI, 0.65–0.97).[531] A similar trend in OS did not reach statistical significance (Table 11, footnote h).[531] Subset analysis suggested that patients expressing high levels of PD-L1 expression treated with nivolumab monotherapy had a similar OS and PFS to patients treated with the more toxic combination therapy (See *PD-L1 Expression*).

Checkmate 067 and 069 also showed substantially increased toxicity with immune checkpoint inhibitor combination therapy versus monotherapy (Table 11). In both trials combination therapy was associated with a much higher rate of discontinuation due to AEs.[408,559] A pooled analysis of these trials found that among patients treated with nivolumab/ipilimumab combination therapy, those who discontinued during the induction phase due to AEs had similar response rates, PFS, and OS as patients who did not discontinue early due to toxicity (but may have continued for other reasons).[560] There are ongoing clinical trials evaluating even lower doses of ipilimumab in combinations in order to mitigate the toxicity while still maintaining the synergy of the combination.[558,561,562]

Kinetics of Response to Combination Therapy

Combination therapy with ipilimumab and nivolumab is associated with improved response rate compared with ipilimumab monotherapy, but as for ipilimumab and nivolumab monotherapy, the apparent median times to response reflect the time to first response assessment (12 weeks).[408] As for nivolumab monotherapy, late complete responses to combination therapy were seen more than a year after the start of treatment: the rate of complete response nearly doubled (increased from 11.5% to 21%) between the first primary report (median follow-up ~12 months) and the most recent analysis (median follow-up 47 months).[408,531] As for single-agent anti-PD-1 therapy, duration of responses were also long. In CheckMate 067 the median duration of response was 50.1 months for combination therapy, and not reached for single-agent nivolumab after a minimum of 48 months follow-up.[531]

Anti-PD-1 Therapy in Patient Subpopulations

BRAF Mutation Status

Subgroup analyses in the Checkmate and KEYNOTE trials showed that 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).[406-408,421,422,523,526,529-531] 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.[408,409,421,528,531]

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 various expression level cutoffs were analyzed to see whether PD-L1 expression levels could be used as a biomarker to predict response to anti-PD-1 therapy.[408,523,526,528,549,563] Across trials, response rate, PFS, and OS for anti-PD-1 therapy tend to improve with increasing PD-L1 expression.[408,410,421,530,531,549,564] However, there were patients who experienced durable responses to anti-PD-1 therapy despite having little or no PD-L1 expression detected in their tumor samples.[408,410,421,526,531,549,564] Analysis of data from Checkpoint 067 showed that although nivolumab efficacy appeared to improve with increasing PD-L1 expression, time-dependent ROC curves indicated that PD-L1 expression alone is an insufficient biomarker to predict OS among patients treated with nivolumab.[531] In trials comparing anti-PD-1 monotherapy to ipilimumab monotherapy, subgroup analyses by PD-L1 expression showed that while response rate, PFS, and OS are higher with anti-PD-1 monotherapy compared to ipilimumab monotherapy for most PD-L1 expression levels, these treatment-dependent differences are smaller among patients with extremely low PD-L1 expression (<1% of cells showing membrane staining).[531,549] None of these analyses, however, were able to identify a PD-L1 expression threshold for selection of an anti-PD-1 agent versus other options.

Among patients treated with nivolumab plus ipilimumab combination therapy, response rate, PFS, and OS tend to increase with increasing PD-L1 expression level.[531,554] Similar to the results for nivolumab monotherapy, ROC curves in Checkmate 067 showed that PD-L1 alone is insufficient for predicting OS among patients treated with nivolumab/ipilimumab combination therapy.[531] Nivolumab/ipilimumab combination improved response rate and outcomes compared with ipilimumab monotherapy for all PD-L1 expression levels tested—including patients with very low PD-L1 expression.[531] Descriptive analyses showed that among patients with low PD-L1 expression, nivolumab/ipilimumab seems to improve outcomes relative to nivolumab monotherapy. Improvements in outcome with combination therapy versus nivolumab monotherapy were not apparent among patients with higher PD-L1 levels.[531] The apparent predictive/prognostic value of PD-L1 is limited by the expression assays and different PD-L1 thresholds across studies. At present, the expression of PD-1 should not be used to exclude patients from anti-PD-1 monotherapy, but may be helpful when choosing between anti-PD-1 monotherapy and ipilimumab/nivolumab combination therapy.

Sequence of Immune Checkpoint Inhibitors

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 increased toxicity but trends toward improved response rate and OS for patients treated with nivolumab followed by ipilimumab compared with patients who received these therapies in the reverse order.[552] Cross-trial comparison suggests that patients who have progressed on ipilimumab have lower response rates and poorer outcomes on anti-PD-1 agents compared with patients who have not had prior systemic therapy (Tables 10–11). Subgroup analyses of data from Keynote-001 and Keynote-006 suggest that pembrolizumab is more effective as a first-line agent than as a second-line agent, even among patients with no prior immune checkpoint inhibitor therapy.[405,549] A retrospective analysis showed responses to pembrolizumab in patients previously treated with ipilimumab is correlated with the patient's prior response to ipilimumab (duration of PFS).[565]

Brain Metastases: Efficacy of Immune Checkpoint Inhibitors

Most prospective randomized trials testing immune checkpoint inhibitors in patients with melanoma and distant metastatic disease have excluded patients with active brain metastases. Although patients with

asymptomatic brain metastasis weren't excluded, for many of these studies the subgroups of patients with brain metastases were very small, and/or data from these subgroups were not reported. Table 12 summarizes the available published efficacy data from samples that included 15 or more patients with brain metastases treated with immune checkpoint inhibitors in prospective clinical trials. Of the 6 studies included in this table, four were studying patients with brain metastases only. Of these, only CA209-170 included a randomized comparison, testing combination therapy verus nivolumab monotherapy in patients with asymptomatic brain metastases.

In aggregate, these trials show that brain metastases can respond to immune checkpoint inhibitors—including ipilimumab monotherapy, anti-PD-1 monotherapy, and ipilimumab/nivolumab combination therapy. What these data do not provide is any robust comparison of agents for treatment of brain metastases—even asymptomatic brain metastases. It is tempting to conclude that nivolumab/ipilimumab combination therapy provides better intracranial responses rates than anti-PD-1 monotherapy, and that anti-PD-1 monotherapy likely provides higher response rates and better OS than ipilimumab monotherapy. However, it is important to note that the populations tested may vary considerably across trials, and that the sample sizes are too small for meaningful statistical comparisons. Several of the trials shown in Table 12 are ongoing (ie, NCT02085070, CA209-170, CheckMate 204), and several other trials testing immune checkpoint inhibitors in patients with brain metastases are planned or ongoing (eg, NCT02460068, NCT03728465, NCT03563729, NCT03340129, NCT02681549).

Table 12. Checkpoint Inhibitor Efficacy in Patients with Brain Metastases: Results from Prospective Trials

Trial			Patients			Treatment Arms	Response Rate[a]		PFS Median (months)[a]		OS Median (months)[a]	
Name and References	Phase Design	Median Follow-up (months)	Prior Sys Tx	Prior Local Brain Tx	Brain Met Symptoms		Extra-cranial	Intra-cranial	Extra-cranial	Intra-cranial		
Ipilimumab												
CA184-042 NCT00623766[136]	II OL	--	78%[b] 71%[b]	41% 48%	None All	HD-ipi (n = 51) HD-ipi (n = 21)	14% 5%	16% 5%	2.6 1.3	1.5 1.2	7.0 3.7	
CA184-169 Subset NCT01515189[544]	III RDB	14.5[c] 11.2[c]	56%[c] 57%[c]	-- --	None	HD-ipi (n = 65) Ipi (n = 62)	-- --	-- --	-- --	-- --	7.0 5.7	NS[d]
Pembrolizumab												
NCT02085070[566,567]	II	11.6	70%[e]	78%[e]	None	Pembro (n = 23)	30%	26%	2		17	
Nivolumab, Nivolumab/Ipilimumab Combination												
CheckMate 037 Subset NCT01721746[410,523]	III R, OL	~24	100%[f]	-- --	None None	Nivo (n = 55) Chemo (n = 18)	-- --	-- --	-- --	-- --	8.7 11.8	NS[g]
CA209-170 NCT02374242[557]	II, R, OL	14 17 31	Some[h] Some[h] Some[h]	None None Some[h]	None None Some	A[i]: Nivo + ipi, then nivo, (n = 36) B[i]: Nivo (n = 27) C[i]: Nivo (n = 16)	57% 29% 25%	46% 20% 6%	13.8 2.6 2.6	NR 2.5 2.3	NR 18.5 5.1	
CheckMate 204 NCT02320058[556]	II	14	17%[j]	Some[j]	None	Nivo + ipi, then nivo (n = 94)	50%	55%	NR	NR	NR	

--, data not reported; Brain Met Symptoms, percent of patients with symptomatic brain metastases; Chemo, Investigator's choice chemotherapy of single-agent dacarbazine or carboplatin/paclitaxel combination; HD-ipi, high-dose ipilimumab (10 mg/kg Q3W); ipi, standard dose ipilimumab (3 mg/kg Q3W); NR, median not reached (further follow-up needed); NS, no significant difference between arms; OL, open-label; pbo, placebo; Prior Sys Tx, percent of patients with prior systemic treatment; Prior local brain tx, percent of patient with prior local treatment for brain metastases (ie, surgery or radiation); R, randomized; RDB, randomized, double-blind; Tx, treatment.

[a] Response rate is the percentage of patients that achieved complete or partial response. P values are for comparisons with the control arm. Median PFS and OS were determined using the Kaplan-Meier method.

[b] In CA182-042, patients with prior checkpoint inhibitor treatment were excluded.

[c] For CA184-169, median follow-up and percent of patients with prior systemic therapy are based on the whole study population (not only those with CNS metastases). Previous systemic therapy was allowed, but patients previously treated with BRAF inhibitors or checkpoint inhibitors were excluded.

[d] For the subset of patients with brain metastases in CA184-169, there was no significant difference in OS between treatment arms (HR, 0.71; 95% CI, 0.49–1.04).

[e] In NCT02085070, some patients had previously been treated with a BRAF inhibitor (n = 4) or ipilimumab (n = 13), but patients previously treated anti-PD-1 or anti-PD-L1 agents were excluded. Patients were required to have at least one brain metastasis that was untreated or unequivocally progressing after local therapy.

[f] Entry criteria for the Checkmate 037 trial stipulated that patients must have progressed on ipilimumab, and if *BRAF* V600 mutation positive, also progressed on a BRAF inhibitor.

[g] For the subset of patients with brain metastases in Checkmate 037, there was no significant difference in OS between treatment arms (HR, 1.42; 95% CI, 0.73–2.76).

[h] In CA209-170, patients were allowed to have previous systemic therapy, but patients were excluded if they had prior treatment with a checkpoint inhibitor. Patients with previous BRAF inhibitor treatment must have intracranial disease progression.

[l] In CA209-170, patients with asymptomatic brain mets, no prior local therapy for brain metastases, and no leptomeningeal disease, were randomized to receive nivo + ipi (cohort A) or nivo alone (cohort B). Patients with brain metastases that had failed local therapy, were symptomatic, and/or had leptomeningeal disease were treated with nivo alone (cohort C). All cohorts were allowed to have had prior systemic therapy.

[j] In CheckMate 204, patients were required to have at least 1 brain metastasis that had not been irradiated and did not require immediate surgery or RT. The study allowed prior local therapy for up to one brain metastasis, limited to SRS or resection. Patients with previous WBRT were excluded. Patients were allowed to have prior adjuvant systemic therapy, but for advanced disease the only prior therapy allowed was IL-2 or IFN-alpha. Seventeen percent had received prior systemic therapy, but this included adjuvant therapy.

Injectable Metastases: Immune Checkpoint Inhibitors Combined with T-VEC Intralesional Injection

Several ongoing trials are testing systemic immune checkpoint inhibitor therapy in combination with T-VEC intralesional injection in patients with unresectable stage IIIB-IV melanoma who have injectable cutaneous, subcutaneous, or nodal metastases (eg, MASTERKEY-265 [NCT02263508], S1607 [NCT02965716], NCT01740297). In all of these trials patients were also allowed to have non-injectable metastases. Reports from phase 1 trials showed promising response rates for combination treatment with T-VEC combined with ipilimumab or pembrolizumab, with no unexpected safety signals (Table 13).[568,569] Results from the phase 2 part of NCT01740297 showed higher response rate among patients randomized to receive T-VEC/ipilimumab combination therapy versus ipilimumab alone (Table 13).[570] Time to response and response duration were indistinguishable between treatment arms. Combination T-VEC plus ipilimumab provided greater reduction in tumor burden not only for injected lesions, but also for some non-injected visceral tumors, suggesting that combination therapy might enhance the systemic response to ipilimumab alone. The impact of this trial on clinical practice is limited, however, both because ipilimumab is not the preferred first-line immune checkpoint inhibitor, and because the improvements in response did not translate into improvements in PFS (Table 13).[570] Follow-up in this study was too short for any comment on the impact of this combination on OS. The incidence of high-grade AEs (grade ≥3) was similar across treatment arms, and the safety profile reflected that observed in prior studies testing T-VEC and ipilimumab as monotherapies, with no unexpected types of toxicities. MASTERKEY-265 includes a phase 3 randomized component comparing pembrolizumab/T-VEC combination therapy with pembrolizumab monotherapy. Results from MASTERKEY-265 are more likely to impact clinical practice because pembrolizumab is among the preferred first-line immune checkpoint inhibitor options.

Table 13: T-VEC Combined with Checkpoint Inhibitors[a]

Trial			Patients		Treatment Arms	Efficacy Results[c]			Grade 3–4 Tx-Related AEs[d]
Name and References	Phase Design	Median Follow-up (months)	Tx Naive	CNS Mets[b]		Response Rate (irRC)	Median PFS (months)	Median OS (months)	
MASTERKEY-265/ Keynote-034 NCT02263508[568]	Ib, OL	18.6	100%	--	T-VEC + Pembro (n = 21)	62%	NR	NR	38%
NCT01740297[569]	Ib, OL	20.0	100%	0%	T-VEC + Ipi (n = 19)	50%	NR	NR	26%
NCT01740297[570]	II, R	15.9	96%	--	T-VEC + Ipi (n = 98)	39% *P* = .002	8.2 *P* = .35	-- NS[e]	45%
		13.5	97%	--	Ipi (n = 100)	18%	6.4	--	35%

--, data no reported; CNS Mets, percent of patients with central nervous system metastases at baseline; ipi, ipilimumab; irRC, immune-related response criteria; NR, not reached (longer follow-up needed); NS, not statistically significant; OL, open label; pembro, pembrolizumab; R, randomized; T-VEC, talimogene laherparepvec intralesional injection; Tx Naïve, percent of patients with no prior treatment for unresectable or distant metastatic disease.

[a] All trials included patients with unresectable stage IIIB-IVM1c disease with injectable lesions (cutaneous, subcutaneous, or nodal).

[b] Patients with active cerebral metastases were excluded from the trials.

[c] Response rate is the percentage of patients that achieved complete or partial response per immune-related response criteria. P values are for comparisons with the control arm. Median PFS and OS were determined using the Kaplan-Meier method.

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

[e] Median OS was not reported, but OS was not significantly different between treatment arms (HR, 0.8; 95% CI, 0.44–1.46).

Immune Checkpoint Inhibitor Administration

The ipilimumab treatment regimen of 3 mg/kg every three weeks for four doses in patients with unresectable or distant metastatic melanoma is well supported by clinical trial data and approved by the FDA.[394,403,404] Furthermore, this is the dose that is approved for use in combination with PD-1 blockade when clinically indicated.

For anti-PD-1 agents, however, there are fewer data to support the optimal dose and duration of treatment. Analyses of randomized cohorts in the KEYNOTE-001 phase I trial showed that there is no clinically meaningful difference in response rate, PFS, and OS for the 3 pembrolizumab regimens tested (ie, 2 mg/kg Q3W, 10 mg/kg Q3W, 10 mg/kg Q2W).[405,550] Results from Keynote-002 and Keynote-006 support this observation (Table 10). Dose-finding trials for nivolumab included patients with a variety of cancer types, and sample sizes for each of the dose levels tested in melanoma patients are too small to be sure of the best dose specifically for patients with melanoma.[571-578]

Table 14 summarizes the treatment dosing and duration used in the pivotal trials supporting anti-PD-1 agents for use in unresectable or metastatic melanoma, as well as the current FDA-recommended dosing. For both nivolumab and pembrolizumab, the FDA-recommended dosing no longer reflects the dosing used in the pivotal trials supporting use of these agents for unresectable or distant metastatic melanoma. Flat dosing regimens for both nivolumab and pembrolizumab were identified by pharmacokinetic models based on data on body weight, exposure, and toxicity from large populations pooled from many trials across a variety of tumor types.[575-577,579,580]

Although the product labels for nivolumab and pembrolizumab indicate that treatment should continue until disease progression or unacceptable toxicity,[395,396] the published trials allowed shorter or longer treatment in certain situations. As mentioned above, long-term follow-up in trials testing anti-PD-1 agents (as monotherapy or in combination with ipilimumab) have shown that responses are very durable, and often persist for years beyond treatment discontinuation.[530,531,551,581] Evidence is accumulating that although most responses to anti-PD-1 therapy develop within 6 months,[406,409,410,528,530,551] there is a notable fraction of responses that take a very long time to develop, and some patients may even experience progression (RECIST-defined) before responding.[406-408,410,421,422,523,526,529-531,549,551,582] Exploratory analyses of phase II/III trials testing nivolumab (Checkmate 037, 066, 067) reported that in highly select patients who per the investigators' discretion were allowed treatment for a limited period beyond progression, subsequent reduction in tumor burden was sometimes observed.[523,526,583] A pooled analysis of data from 8 clinical trials found that in patients receiving anti-PD-1 agents (either alone or in combination) treatment beyond RECIST-defined progression resulted in further reduction in tumor burden by 30% or more in 19% of patients, as well as improvement in OS for patients treated beyond progression versus those who discontinued treatment at the time of progression.[584] Other exploratory analyses of trials have shown that early discontinuation of anti-PD-1 therapy (ie, due to AEs) does not impact clinical outcomes,[531,560] and that responses can occur after discontinuation.[560] It is unclear whether treatment beyond progression was really responsible for the positive outcomes observed. Prospective randomized trials are needed to determine the duration of anti-PD1 treatment needed to optimize clinical benefit and minimize risk of toxicity.

Table 14. Immune Checkpoint Inhibitor Treatment Regimens

	Dosing	Treatment Duration
Nivolumab		
CheckMate 066[526]	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[408]		
CheckMate 037[523]		
FDA Prescribing information[395]	240 mg Q2W or 480 mg Q4W	Until disease progression or unacceptable toxicity.
Pembrolizumab		
KEYNOTE-002[406]	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[407]	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.
FDA Prescribing information[396]	200 mg Q3W	Until disease progression or unacceptable toxicity.
Ipilimumab/Nivolumab Combination		
CheckMate 067[408]	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[528]		
FDA Prescribing information[585]	1 mg/kg nivo + 3 mg/kg ipi (same day), Q3W for 4 doses; then 240 mg Q2W or 480 mg Q4W	Until disease progression or unacceptable toxicity.

CR, complete response; Ipi, ipilimumab; nivo, nivolumab; PD, progressive disease; Q2W, once every 2 weeks; Q3W, once every 3 weeks.

Toxicity of Immune Checkpoint Inhibitors

Most of the treatment-related AEs associated with immune checkpoint inhibitors are autoimmune in nature. The array of immune-related toxicities associated with immune checkpoint inhibitors (across all cancer types), as well as recommendations for management of each, can be found in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities. Table 15 lists types and rates for the most common toxicities seen in prospective randomized trials that compared immune checkpoint inhibitors in patients with unresectable stage III or stage IV cutaneous melanoma.

Across all three immune checkpoint inhibitor options shown in Table 15 (ipilimumab, anti-PD-1 monotherapy, ipilimumab/nivolumab combination therapy), the most common AEs were cutaneous toxicities (rash, pruritus, maculopapular rash, 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, adrenal insufficiency, hypo- or hyperthyroidism), pancreatitis (elevated lipase and amylase), and hepatic AEs (eg, elevated ALT/AST, hepatitis).[394] Other less common but

potentially life-threatening high-grade immune-related toxicities include nephritis, pneumonitis, and myocarditis. Management of these unusual events is summarized in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities. Analysis of the WHO pharmacovigilance database, including patients treated with immune checkpoint inhibitors for any indication, found that for patients treated with anti-CTLA-4, colitis caused the most AE-related deaths, whereas AE-related deaths for anti-PD-1/PD-L1 agents were most often from pneumonitis, hepatitis, and neurotoxic effects.[586] AE-related deaths in patients treated with combination PD-1/CTLA-4 inhibitors were most frequently from colitis or myocarditis.[586]

Although there are no data from prospective randomized trials directly comparing nivolumab versus pembrolizumab, these agents appear to have similar safety profiles (Table 15). Safety results from randomized phase II-III trials showed that combination therapy with nivolumab and ipilimumab was associated with more toxicity than single-agent ipilimumab or nivolumab (Table 15).[408,409,528,531] 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 15) and AEs leading to treatment discontinuation (40% for nivolumab/ipilimumab combination vs. 13% for nivolumab monotherapy, 15% for ipilimumab monotherapy).[531] Table 15 shows that many of the common toxicities were more frequent or more often high grade with combination ipilimumab plus anti-PD-1 regimens than with immune checkpoint inhibitor monotherapy. Although earlier reports suggested that anti-PD-1 monotherapy was associated with less toxicity than ipilimumab, these differences appear to be less significant with longer term follow-up (Table 15).[407-409,422,528,531]

Kinetics of Immune-Related Toxicities

Pooled analyses of data from prospective trials testing immune checkpoint inhibitors in patients with unresectable or distant metastatic melanoma show that time to onset and time to resolution differ across different types of AEs.[587,588] Most skin-related AEs manifest early, but risk of developing a cutaneous AE persists throughout treatment. Among high-grade AEs, gastrointestinal and hepatic toxicities tend to take a bit longer to develop (than cutaneous AEs), followed by pulmonary, endocrine, and renal AEs. Although these trends are clear, for many irAEs the ranges of time to onset are quite broad. Although uncommon, initial irAEs have been observed up to a year following initiation of treatment. Median time to resolution is similar for most types of common high-grade AEs, on the order of months, but endocrine AEs may not resolve. Up to 20% of high-grade cutaneous AEs also appear to persist indefinitely.[587,588] Analysis of the WHO pharmacovigilance database found that fatal AEs associated with immune checkpoint inhibitors (all indications) usually occurred within the first 2 months of treatment.[586]

Table 15. Checkpoint Immunotherapies: Treatment-Related Toxicities[a]

Study:	CheckMate 067 and 069[409,531]						KEYNOTE-006[407,422]			
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	20–28	86–94	22	86	54–59	90–96	20[c]	73–74[c]	12–17[c]	76–80[c]
Diarrhea	6–11 ***		3 **		10 *****		3[c] **[c]		2–3[d] **[c]	
Colitis	2–8 *		1		8–13 **		6 *		3	
Nausea	1–2 **		0 *		1–2 ***		<1[c] *[c]		<1[c] *[c]	
Vomiting	<1 *		<1 *		1–2 **		0 *		<1	
Decreased appetite	<1 *		0 *		≤1 **		0 *		0 *	
Rash	≤2 ***		<1 **		3–4 ****		≤1[c] **[c]		0[c] **[c]	
Pruritus	<1 ****		<1 **		1–2 ****		<1[c] ***[c]		0[c] **[c]	
Maculopapular rash	<1 *		1 *		2–3 **		<1		<1	
Vitiligo	0[b] *[b]		<1 *		0[b] *		0		0 *	
Fatigue	≤1 *****		1 ****		4–5 ****		1[c] **[c]		≤1[c] ***[c]	
Pyrexia	<1 *		0 *		1–3 **		0		0	
Arthralgia[b]	0[b] *[b]		<1[b] *		1 *[b]		≤1[c] *[c]		<1[c] *[c]	
Myalgia	0 *		<1 *		<1 *		<1		<1	
Asthenia	1[b] *[b]		<1 *		<1[b] *[b]		1 *		<1 *	
Headache	<1 *		0 *		1–2 *		0		0	
Dyspnea	0		<1 *		1–2 *		<1		<1	
Cough	0 *		1 *		0 *		0		0	
Abdominal pain	1–2 *		0 *		<1 *		0 *		0	
Chills	0 *		0		0 *		0		0	
Elevated ALT	≤2 *		1		9–11 ***		1		<1	
Elevated AST	≤1 *		1		6–7 ***		1		<1	
Hypophysitis	2–4 *		<1		2 *		1		<1	
Hypothyroidism	0 *		0 *		<1 **		0[c] [c]		<1[c] *[c]	
Hyperthyroidism	0[b]		0		1[b] *[b]		<1		0	
Elevated lipase	≤4 *		5 *		10–11 **		-- --		-- --	
Elevated amylase	≤1		2 *		2–3 *		-- --		-- --	
Pneumonitis	<1		<1		1–2 *		-- --		-- --	
Creatinine increased	0		<1		≤1		0		0	

--, not reported

[a] Specific AEs listed occurred in ≥10% of patients for at least one checkpoint immunotherapy regimen. This table shows percent of patients who experienced at least one AE of any grade, grade 3–4, or grade 3–5. For the any grade column, 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. Blank indicates that <5% of patients experienced that AE.

[b] Data available from only one of two trials.

[c] For KEYNOTE-006, unless otherwise noted data shown are from the first interim analysis based on median follow-up of 7.9 months. Footnote indicates data from a later report based on median 22.9 months follow-up. The later report did not include a complete AE listing.[422]

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).[90,589] BRAF inhibitors have been shown to have clinical activity in unresectable metastatic melanomas with *BRAF* V600 mutations. Co-administration of inhibitors of MEK, a signaling molecule downstream of BRAF, potentiates these effects. 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 unresectable advanced melanoma.

BRAF Inhibitor Monotherapy

Vemurafenib and dabrafenib were developed to inhibit BRAF with mutations at V600.[590-592] For patients with previously untreated stage IV or unresectable stage III melanoma with *BRAF* V600 mutations, phase III trials (ie, BRIM-3, BREAK-3) have shown that monotherapy with either of these agents improves response rates, PFS, and OS compared with chemotherapy (dacarbazine; Tables 17–18). For both vemurafenib (Table 16) and dabrafenib (Table 17), efficacy in patients with previously treated unresectable 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 (ie, BRIM-3, BREAK-3). Phase III trial results show that time to response for BRAF inhibitors (median ~1.5 months) may be shorter than with chemotherapy.[92,94,95] Responses to BRAF inhibitor monotherapy are relatively short lived, however, with median duration ~5 to 10 months.[94,412,525,593-597] Likewise, PFS and OS Kaplan-Meier curves for vemurafenib and dabrafenib show little or no decline during the first few months of treatment (ie, ~1.5 months for PFS, ~3 months for OS), and then abruptly begin to decline.[93,94]

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

Trial			Patients			Treatment Arms	Efficacy Results[b]			AEs by Grade[c]		
Name and References	Phase Design	Median Follow-up (months)	Prior BRAFi	Tx Naive	Brain Mets		Response Rate	Median PFS (months)	Median OS (months)	3	4	5
NCT00949702[a593]	II OL	12.9	0	0	<1%	Vem (n = 132)	53%	6.8	15.9	60%	4%	<1%
BRIM-3 NCT01006980[92,93,598]	III R, OL	13.4; 12.5[d]	0	100%	NR[e]	Vem (n = 337)	48%	6.9	13.6	67%	7%	2%
		9.2; 9.5[d]	0			DTIC (n = 338)	5% *P* < .001	1.6 *P* < .0001	9.7 *P* = .003	33%	9%	1%
NCT01307397[525,594]	IV OL	32.2	0	50%	23%[e]	Vem (n = 3222)	36%	5.6	12.1	53%		4%

--, data not reported; *BRAF* V600E (K), percent of patients with a *BRAF* V600E (percent with *BRAF* V600K); BRAFi, BRAF inhibitor; Brain Mets, percent of patients with brain metastases at baseline; DTIC, dacarbazine; R, randomized; OL, open label; Tx Naïve, percent of patients with no prior treatment for unresectable or distant metastatic disease; vem, vemurafenib.

[a] Unresectable stage IIIC or stage IV melanoma; NCT00949702 included only stage IV melanoma. All patients had a *BRAF* V600 mutation. *BRAF* mutations reported were V600E (91%–92%), V600K (8%–9%) or not reported.

[b] Response rate is the percentage of patients that achieved complete or partial response. P values are for comparisons with the control arm. Median PFS, median OS, and P value determined using the Kaplan-Meier method. P values are for comparisons with the control arm.

[c] For BRIM-3 and NCT01307397, rates show percent of patients with ≥1 AE of any cause (treatment or otherwise). For NCT00949702, rates reflect percent of patients ≥1 treatment-related AE.

[d] Median follow-up for OS and safety analysis; response and PFS.

[e] Patients with active CNS metastases were excluded from these trials.

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

Trial			Patients			Treatment Arms	Efficacy Results[b]			Grade 3–4 AEs[c]
Name and References	Phase Design	Median Follow-up (months)	Prior BRAFi	Tx Naive	Brain Mets		Response Rate	Median PFS (months)	Median OS (months)	
BREAK-2 NCT01153763[595]	II OL	11.9	0	16%	0%	Dab (n = 92)	59% (13%)[d]	6.3 (4.5)[d]	13.1 (12.9)[d]	27%
BREAK-3 NCT01227889[94,95]	III R, OL	15.2	0	100%	0%	Dab (n = 187)	50%	5.1 *P* < .0001	18.2 HR = 0.76	53%[e]
		12.7	0			DTIC (n = 63)	5%	2.7	15.6	44%[e]

--, data not reported; *BRAF* V600E (K), percent of patients with a *BRAF* V600E (percent with *BRAF* V600K); BRAFi, BRAF inhibitor; Brain Mets, percent of patients with brain metastases at baseline; dab, dabrafenib; DTIC, dacarbazine; R, randomized; OL, open label; Tx Naïve, percent of patients with no prior treatment for unresectable or distant metastatic disease.

[a]Stage IV melanoma; BREAK-3 also included unresectable stage III. All patients had a *BRAF* V600 mutation. *BRAF* mutations reported were V600E (83%–100%) or V600K (0%–17%).

[b] Response rate is the percentage of patients that achieved complete or partial response. P values are for comparisons with the control arm. Median PFS and OS, P value, and HR were determined using the Kaplan-Meier method.

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

[d] Data shown are from patients with *BRAF* V600E (V600K) mutation.

[e] Percent of patients with AEs of grade 2 or greater. Rates of adverse events of grade ≥3 were not reported.

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Table 18. Encorafenib Monotherapy in Advanced Melanoma[a]

Trial			Patients			Treatment Arms	Efficacy Results[b]			Grade 3–4 AEs[c]
Name and References	Phase Design	Median Follow-up (months)	Prior BRAFi	Tx Naive	Brain Mets		Response Rate	Median PFS (months)	Median OS (months)	
NCT01436656[599]	I, dose escalation	--	0	--	--[d]	Encor (n = 25)	60%	--	--	70%
			100%	0	--[d]	Encor (n = 29)	10%	--	--	
	I, dose expansion	--	0	--	--[d]	Encor (n = 15)	60%	12.4	NR	--
			100%	0	--[d]	Encor (n = 18)	22%	1.9	9.07	--

--, data not reported; *BRAF* V600E (K), percent of patients with a *BRAF* V600E (percent with *BRAF* V600K); BRAFi, BRAF inhibitor; Brain Mets, percent of patients with brain metastases at baseline; Encor, encorafenib; NR, not reached; Tx Naïve, percent of patients with no prior treatment for unresectable or distant metastatic disease.

[a] Unresectable stage IIIB-IV melanoma. All patients had a *BRAF* V600 mutation. *BRAF* V600E was reported in 87%–94% of patients.

[b] Response rate is the percentage of patients that achieved complete or partial response. Median PFS and OS were determined using the Kaplan-Meier method.

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

[d] Asymptomatic/inactive brain metastases were allowed but not reported.

BRAF/MEK Inhibitor Combination Therapy

Despite high initial response rates, half of the patients treated with BRAF-targeted monotherapies relapse within 6 months, due to development of drug resistance.[94,412,525,593-597] Alternate methods for targeting the MAP kinase pathway are being explored as options for overcoming resistance to BRAF inhibitor therapy. Trametinib, cobimetinib, and binimetinib 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.[600] 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.[593,92,94] Moreover, in an open-label, phase II study, trametinib failed to induce objective responses in 40 patients previously treated with a BRAF inhibitor.[601] Binimetinib has also been shown to provide improved response rates and PFS compared with DTIC in a phase 3 randomized trial in patients with unresectable stage IIIC or stage IV melanoma with NRAS Q61R/K/L mutations.[602] Nonetheless the ORR (15%) and PFS (median 2.8 months) for patients treated with binimetinib were poor compared to those for BRAF inhibitors tested in other trials.

Although MEK inhibitor monotherapy has limited utility for treating advanced metastatic melanoma, several 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 distant metastatic disease (Table 19).[411-413,597,603,604] When compared with either single-agent dabrafenib or single-agent vemurafenib, BRAF/MEK inhibitor combination therapy with dabrafenib and trametinib or vemurafenib plus cobimetinib improved response rate, duration of response, PFS, and OS.[411-413,597] A recent phase 3 randomized trial (COLUMBUS) showed that encorafenib, a BRAF inhibitor, when combined with the MEK inhibitor binimetinib, improves PFS and OS compared with vemurafenib monotherapy.[605,606] Patients in the COLUMBUS trial were treatment naïve or had progressed on or after previous first-line immunotherapy; no other prior therapies for locally advanced, unresectable, or metastatic melanoma were allowed. This trial also compared encorafenib/binimetinib combination therapy versus encorafenib monotherapy, but the improvements in PFS and OS did not reach statistical significance. Although across trials of patients with previously untreated metastatic disease, vemurafenib monotherapy and dabrafenib monotherapy have resulted in roughly similar response rates and PFS;[92-95,411-413,597,598,603,604] results from the COLUMBUS trial showed that encorafenib monotherapy improved PFS and OS compared with vemurafenib monotherapy.[605,606]

The efficacy of BRAF/MEK inhibitor combination therapy in patients with previously treated advanced melanoma is a topic of ongoing research. Results from phase I/II studies (Table 19) showed that in patients who have received previous BRAF inhibitor treatment, subsequent BRAF/MEK inhibitor combination therapy was associated with a relatively poor response rate, PFS, and OS, compared with patients who had not received prior BRAF inhibitor treatment.[527,607-611] Likewise, although encorafenib improved response rate and PFS compared with vemurafenib in patients with no prior BRAF inhibitor treatment (Table 19), data from a phase 1 trial suggest that patients with prior dabrafenib or vemurafenib treatment still have fairly low response rates and poor PFS when treated with encorafenib (Table 18).[599] However, emerging data suggest that resistance to BRAF-targeted therapy may not be as irreversible as previously thought. 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. 26%; median PFS: 1.8 months vs. 3.9 months, *P* = .018).[527] One single-arm phase II study (NCT02296996) that restricted enrollment to patients who had previously progressed on BRAF-targeted therapy, and progressed on anti-CTLA-4 or anti-PD-1, and had least 12 weeks since finishing their last BRAF-targeted treatment, found that response rate was relatively high (32%) compared with other prospective studies that tested BRAF/MEK inhibitor therapy in patients who previously progressed on BRAF-targeted therapy (response rate 10%–15% in BRIM-7, NCT01072175, NCT01619774; see Table 19).[527,610,611] Some of the patients who responded to rechallenge had previously progressed on BRAF/MEK inhibitor combination therapy.[611] These results from NCT01072175 and NCT02296996 suggest that resistance to BRAF-targeted therapy may be reversible, at least in some patients. Identification of the best candidates for retreatment is a topic of ongoing research.

Across trials, the apparent time to response for all BRAF/MEK inhibitor combinations reflects the time to first tumor response assessment (6 weeks in BRIM-7, 8 weeks in other trials).[413,596,605,607] Results from multiple randomized trials suggest that BRAF/MEK inhibitor combination therapy may improve duration of response compared with BRAF inhibitor monotherapy, although the magnitude of this effect varies, with increases in median duration of response ranging from 2 to 6 months.[412,596,597,603,606]

Table 19. BRAF/MEK Inhibitor Combination in Advanced Melanoma[a]: Key Trials

Trial			Patients			Treatment Arms	Efficacy Results[b]						AEs Grade 3–4[c]
Name and References	Phase Design	Median follow-up (months)	Prior BRAFi	Tx Naive	Brain Mets		Response Rate		Median PFS (months)		Median OS (months)		
BRIM-7[607-609] NCT01271803	Ib OL, dose escalation	26	0[d]	Some[d]	NR[e]	Vem + cobi (n = 63)	87%		13.8		31.2		78%
		8	100%[d]	0[d]		Vem + cobi (n = 66)	15%		2.8		8.5		47%
NCT02296996[611]	II OL	6.8	100%[f]	0	68%	Dab + tram (n = 25)	32%		4.9		NR		8%
NCT01072175[527]	I/II OL	35.3	100%[g]	0	23%	Dab + tram (n = 26)	15%		3.6		10.0		61%
		27.4	100%[g]	0	9%	Dab + tram (n = 45)	13%		3.6		11.8		44%
NCT01072175 Part C[596,612]	II R	66.5	0	Some[h]	4%[e]	Dab (150 mg BID) + tram (2 mg QD) (n = 54)	76%	*P* = .03	9.4	*P* < .001	25.0		67%
			0		13%[e]	Dab (150 BID) + tram (1 mg QD) (n = 54)	50%	*P* = .77	9.2	*P* = .006	22.5		54%
			0		7%[e]	Dab (150 mg BID)	54%		5.8		20.2		47%
NCT01619774[610]	II	5.9	100%[g]	0	--[e]	Dab + tram (n = 23)	10%		3.0		10.2		71%
COMBI-d[411,603] NCT01584648	III RDB	20	0	100%	--[e]	Dab + tram (n = 211)	69%	*P* = .0014	11.0	*P* = .0004	25.1	*P* = .0107	48%[i]
		16	0			Dab + pbo (n = 212)	53%		8.8		18.7		50%[i]
COMBI-v[412] NCT01597908	III R, OL	11	0	100%	--[e]	Dab + tram (n = 352)	64%	*P* < .001	11.4	*P* < .001	NR	*P* = .005	52%
		10	0			Vem (n = 352)	51%		7.3		17.2		63%
Co-BRIM[413,597,604] NCT01689519	III RDB	14.2; 18.5[j]	0	100%	<1%[e]	Vem + cobi (n = 247)	70%	*P* < .0001	12.3	*P* < .0001	22.3	*P* = .005	75%
			0		<1%[e]	Vem + pbo (n = 248)	50%		7.2		17.4		61%
COLUMBUS[605,606] NCT01909453	III R, OL	32.1 (PFS) 36.8 (OS)	0	70%[k]	5%[e]	Encor + bini (n = 192)	64%		14.9	*P* < .0001[l]	33.6	*P* < .0001[l]	64%
			0	70%[k]	--[e]	Encor (n = 194)	52%		9.6	*P* = .0038[l]	23.5	*P* = .033[l]	67%
			0	70%[k]	2%[e]	Vem (n = 191)	41%		7.3		16.9		66%

--, data not reported; bini, binimetinib; *BRAF* V600E (K), percent of patients with a *BRAF* V600E (percent with *BRAF* V600K); BRAFi, BRAF inhibitor; Brain Mets, percent of patients with brain metastases at baseline; cobi, cobimetinib; dab, dabrafenib; encor, encorafenib; NR, not reached; OL, open label; R, randomized; RDB, randomized double-blind tram, trametinib; Tx Naïve, percent of patients with no prior treatment for unresectable or distant metastatic disease; vem, vemurafenib.

[a] Unresectable (AJCC 7th Edition) stage IIIC or stage IV melanoma. COLUMBUS also included patients with (AJCC 7th Edition) stage IIIB disease. All patients had a *BRAF* V600 mutation. *BRAF* mutations reported were V600E (83%–92%), V600K (4%–17%), or not reported.

[b] Response rate is the percentage of patients that achieved complete or partial response. P values are for comparisons with the control arm. Median PFS and OS, P value, and HR were determined using the Kaplan-Meier method.

[c] Percent of patients with grade 3–4 AEs of any cause (treatment or otherwise).

[d] BRIM-7 included a cohort of patients who had recently progressed on vemurafenib (n = 66) and a cohort of patients with no prior BRAF inhibitor (n = 63). Each may have had other types of prior systemic therapy. For the latter, the number without any prior treatment was not reported.
[e] Patients with active brain metastases were excluded from the trial. Treated stable brain metastases were allowed.
[f] In NCT02296996, patients were required to have progressed on prior BRAF inhibitor therapy (or BRAF/MEK inhibitor combination therapy) and to have progressed on prior anti-CTLA-4 or anti-PD-1 checkpoint inhibitor therapy.
[g] Johnson 2014[527] reported results from two cohorts in NCT01072175 consisting of patients who progressed on prior BRAF inhibitor monotherapy. Patients in NCT01619774 were required to have progressed on prior BRAF inhibitor monotherapy.
[h] In Part C of NCT01072175, all patients had no prior BRAF or MEK inhibitor treatment, but some had prior chemotherapy (13% vs. 28% vs. 22%) and some had prior immunotherapy (24% vs. 30% vs. 15%). The number with no prior systemic therapy was not reported.
[i] Based on analysis after ≥36-month follow-up for all living patients.
[j] Co-BRIM median follow-up shown for response and PFS analysis; OS and safety analysis.
[k] In COLUMBUS, 30% of patients in each arm had prior systemic immunotherapy, mostly IFN or interleukins. Other types of prior systemic therapy were not allowed.
[l] In COLUMBUS, encorafenib/binimetinib combination therapy versus encorafenib monotherapy did not result in significantly different PFS (HR, 0.75; 95% CI, 0.56–1.00; *P* = .050) or OS (HR, 0.81; 95% CI, 0.61–1.06; *P* = .12).

BRAF-Targeted Therapies for Brain Metastases

As shown in tables 17, 18, and 20, patients with active brain metastases were excluded from prospective comparative trials testing BRAF-targeted therapies. Patients with stable asymptomatic brain metastases were sometimes allowed, but for many of these studies this subpopulation was small. Several prospective non-comparative trials have tested single-agent dabrafenib, single-agent vemurafenib, and dabrafenib/trametinib combination in patients with brain metastases (Table 20).[594,613-616] Some of these studies included patients with symptomatic brain metastases,[613,614,616] and some included patients whose intracranial disease had progressed after local therapy.[614-616] All of the studies shown in Table 20 included patients who had prior systemic therapy for metastatic disease, but most excluded patients with prior BRAF inhibitor therapy. Results from these trials show that melanoma brain metastases can respond to BRAF inhibitor monotherapy or BRAF/MEK inhibitor combination therapy, albeit with lower response rates than for extracranial disease. It is notable that intracranial responses were seen even among patients with prior systemic therapy for metastatic disease, symptomatic brain metastases, and intracranial progression after local therapy, as these populations tend to be difficult to treat. One of the studies in patients with symptomatic brain metastases also reported symptomatic improvement based on reduction in use of corticosteroids and increase in performance score.[613] Results from COMBI-MB suggest that among patients with brain metastases, dabrafenib/trametinib combination therapy may provide higher rates of response than single-agent BRAF inhibitor therapy. However, cross-trial comparisons in studies of patients with brain metastases are particularly difficult because there are a number of factors that may profoundly impact measured outcomes—including extent and location of intracranial disease, severity of symptoms, and number and type of prior systemic and local intracranial therapies. Prospective randomized trials are needed to determine which BRAF-directed therapy options provide the best results in patients with brain metastases.

Table 20. BRAF/MEK Inhibitor Efficacy in Patients with Brain Metastases: Results from Prospective Trials

Trial			Patients[a]				Treatment Arms	Response Rate[b]		PFS Median (months)[b]		OS Median (months)[b]
Name and References	Phase Design	Median Follow-up (months)	Prior BRAFi	Prior Sys Tx	Prior local Brain Tx	Brain Met Symptoms		Extra-cranial	Intra-cranial	Extra-cranial	Intra-cranial	
NCT01253564[613]	Pilot, OL	--	0	83%	79%	100%	Vem (n = 24)	62%	16%	3.8		5.3
MO25515 Subset[525,594] NCT01307397	IV, OL	32.2[b]	1%[c]	50%[c]	--[c]	0	Vem (n = 753)	24%		3.7		7.4
McArthur 2017[614]	II	9.6	0	20%	0	Some[e]	1: Vem (n = 90)	33%	18%	--	3.7	8.9
			0	30%	100%[d]		2: Vem (n = 56)	23%	18%	--	4.0	9.6
BREAK-MB NCT01266967[615]	II OL	≥4	0	≥26%[f]	0	0	A: Dab (n = 89)	38% (0)[g,h]	39% (7%)[g]	3.8 (1.9)[g]		7.7 (3.8)[g]
		≥4	0	≥42%[f]	100%[c]	0	B: Dab (n = 83)	31%[f] (28%)[g,h]	31% (22%)[g]	3.9 (3.7)[g]		7.3 (5.1)[g]
COMBI-MB NCT02039947[616]	II, OL	8.5	0	22%[i]	0	0	A: Dab + Tram (n = 76)	55%	58%	5.6		10.8
		20.0	0	31%[i]	100%[c]	0	B: Dab + Tram (n = 16)	44%	56%	7.2		24.3
		9.5	0	19%[i]	Some[c]	0	C: Dab + Tram (n = 16)	75%	44%	4.2		10.2
		11.0	0	41%[i]	Some[c]	100%	D: Dab + Tram (n = 17)	41%	59%	5.5		11.5

--, data not reported; Brain Met Symptoms, percent of patients with symptomatic brain metastases; OL, open-label; Prior Sys Tx, percent of patients with prior systemic treatment; Prior local brain tx, percent of patient with prior local treatment for brain metastases (ie, surgery or radiation); Tx, treatment.

[a] All patients had a *BRAF* V600 mutation. *BRAF* mutations reported were V600E (83%–100%), V600K (4%–22%), or not reported.

[b] Response rate is the percentage of patients that achieved complete or partial response. Median PFS and OS were determined using the Kaplan-Meier method.

[c] For MO25515, the median follow-up and percent of patients with prior systemic treatment shown are for the whole patient population, not only those with brain metastases. Prior local treatment for brain metastases was allowed, but the number of patients with prior RT or surgery for brain metastases was not reported.

[d] Patients with prior local treatment for brain metastases were required to have intracranial progression.

[e] Trial allowed patients with symptomatic or asymptomatic brain metastases.

[f] BREAK-MB included patients with up to 2 prior systemic treatments, excluding BRAF or MEK inhibitors. For cohorts A and B, respectively, 26% and 42% had prior chemotherapy, and 6% and 17% had prior immunotherapy.

[g] For response, PFS, and OS from BREAK-MB, data are reported for patients with *BRAF* V600E (V600K).

[h] Extracranial response was not reported for BREAK-MB. Data shown are for overall response.

[l] COMBI-MB included patients with up to 2 prior systemic treatments, excluding BRAF or MEK inhibitors. Prior temozolomide and adjuvant interferon were not counted as prior systemic treatments.

BRAF and MEK Inhibitor Safety

Table 21 summarizes the safety data from phase III trials comparing BRAF/MEK inhibitor combination therapy to BRAF inhibitor monotherapy. The risk of toxicity (all grade, grade 3–5) was similar for BRAF/MEK inhibitor combination therapy compared with single-agent BRAF inhibitor therapy, and BRAF inhibitor monotherapies (ie, vemurafenib, dabrafenib, encorafenib) and BRAF/MEK inhibitor combinations (ie, dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib), were associated with high rates of flu-like symptoms: pyrexia and chills, fatigue and asthenia, headache, various types of musculoskeletal aches and pains (eg, arthralgia, myalgia), and gastrointestinal upset (eg, diarrhea, nausea, vomiting).[412,524,597,603,606] Whereas BRAF/MEK inhibitor combination therapy was associated with higher risk of pyrexia and diarrhea, BRAF inhibitor monotherapy was associated with higher risk of musculoskeletal complaints. Alopecia, rash, and other skin toxicities are also common across all types of BRAF-targeted therapy, but in phase III trials most of these toxicities were actually more common with BRAF inhibitor monotherapy versus BRAF/MEK inhibitor combination therapy. Hyperproliferative skin toxicities had notably higher prevalence in patients treated with BRAF inhibitor monotherapies versus BRAF/MEK inhibitor combinations, including hyperkeratosis, palmoplantar disorders, keratoacanthoma, and cutaneous squamous cell carcinoma. Due to better efficacy and a different toxicity profile, specifically lower risk for certain proliferative skin toxicities, BRAF/MEK inhibitor combination therapy is generally preferred over BRAF inhibitor monotherapy. In clinical practice across NCCN Member Institutions, the change in prescribing patterns from using BRAF inhibitor monotherapy to using BRAF/MEK inhibitor combinations has resulted in lower rates of discontinuation due to hypoproliferative skin toxicities and musculoskeletal complaints; flu-like symptoms are still very common (with BRAF/MEK inhibitor combination) but seem less likely to lead to discontinuation of treatment, especially if patients are forewarned. There are rare patients who experience certain toxicities on BRAF/MEK inhibitor combination therapy that are thought to be attributed to MEK inhibitors (eg, deep venous thrombosis, retinal problems, concerns about immunosuppression), and in those cases discontinuation of the MEK inhibitor may be helpful. There are few data to inform selection among the BRAF/MEK inhibitor combination therapy options (ie, dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib), as none of the options have been directly compared.

Grade 5 toxicities were rare (≤2% in phase III trials) in trials testing BRAF inhibitor monotherapy or BRAF/MEK inhibitor combination therapies.[412,593-598,603,606,607] Grade 5 AEs observed across trials included cardiovascular or cerebrovascular events (eg, brain/intracranial hemorrhage, brain ischemia, acute coronary syndrome, cardiac arrest/failure, acute myocardial infarction, pulmonary embolism), AEs related to infection (eg, pneumonia, pleural infection, sepsis), and multi-organ failure. [412,594,596,597,603,606] It is not clear which of these grade 5 AEs were really related to treatment. In addition to those shown in Table 21, reports from multiple clinical trials have highlighted a few other rare high-grade AEs of special interest, including an assortment of ocular AEs (eg, retinopathies, blurred vision, retinal detachment, uveitis), QT prolongation, decreased ejection fraction, thrombotic events, and the development of new primary malignancies.[92,412,525,527,603-605,607,617]

Analysis of data from the several prospective trials showed that for BRAF-targeted therapy, most AEs manifest within the first few months of therapy, although AEs continue to develop throughout treatment, albeit at a lower rate.[525,596,604,605] There is some evidence to suggest that time to onset may be longer for BRAF/MEK inhibitor combination therapy compared with BRAF inhibitor monotherapy, at least for some types of AEs.[604,605] In the COLUMBUS trial, median time to first occurrence of grade 3–4 toxicity was longer with encorafenib/binimetinib combination versus encorafenib or

vemurafenib monotherapy (8.4 vs. 2.8, 3.7 months).[605] In Co-BRIM, some of the most common AEs had early onset in both arms (eg, pyrexia, rash, elevated creatine phosphokinase [CPK], liver function test [LFT] abnormality), whereas diarrhea was quick to develop in the cobimetinib/vemurafenib combination therapy arm, but took longer to develop in the vemurafenib monotherapy arm.[604] Regardless of treatment, cutaneous squamous cell carcinoma (cSCC)/keratoacanthoma, photosensitivity, serous retinopathy, and left ventricular ejection fraction (LVEF) decline tended to have wider ranges of time to onset (and therefore longer median time to onset) than other types of AEs.[604] Results from a large stage IV trial testing vemurafenib also reported that time to onset for cSCC was longer than for other types of AEs.[525] Results from the Co-BRIM trial suggest that for these cutaneous AEs and ocular AEs, median time to onset was longer with cobimetinib/vemurafenib versus vemurafenib monotherapy.[604] Time to resolution varied across different type of AEs and type of treatment, although the majority resolved within 3 months.[604]

Table 21. BRAF and MEK Inhibitors: Toxicities[a]

Studies:	COMBI-d[b,524,603]				COMBI-v[412]				Co-BRIM[597]				COLUMBUS[606]					
Agent:	Dab		Dab/Tram		Vem		Dab/Tram		Vem		Vem/Cobi		Vem		Encor		Encor/Bini	
Grade:	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–4[c]	Any	3–4[c]	Any	3–4[c]	Any
All types	50	97	48	97	59	99	49	98	61	98	75	99	66	--	67	--	64	--
General, symptomatic:																		
Pyrexia	2	***	7	******	1	**	4	*****	0	**	1	***	0	***	1	*	4	**
Chills	1	**	1	***	0	*	1	***	0	*	0	*	--	--	--	--	--	--
Headache	1	***	1	***	1	**	1	***	2	**	<1	**	1	**	3	***	2	***
Fatigue	1	****	2	****	2	***	1	***	3	***	5	****	2	***	1	***	2	***
Asthenia	1[b]	*b	<1[b]	*b	1	**	1	**	1	**	2	**	4	**	3	**	2	**
Decreased appetite	1[b]	*b	<1[b]	*b	0	**	1	*	<1	**	0	**	1	**	1	**	0	*
Peripheral edema	1	*	1	**	<1	*	<1	*	<1	*	0	*	1	*	0	*	2	*
Cough	0	**	0	**	0	*	0	**	0	*	0	*	1	*	1	*	1	*
General, lab results:																		
Hypertension	6	**	6	**	10	**	14	***	3	*	6	**	3	*	3	*	6	*
ALT increased	1	*	2	*	4	**	3	*	6	**	11	***	2	*	1	*	5	*
AST increased	1		3	*	3	*	1	*	2	*	9	**	2	*	1		2	*
GGT increased	--	--	--	--	--	--	--	--	10	**	15	**	3	*	5	*	9	**
Blood CPK increased	--	--	--	--	--	--	--	--	<1		12	****	0		0		7	***
Blood ALP increased	--	--	--	--	--	--	--	--	2	*	5	**	1	*	0		1	*
Lipase increased	--	--	--	--	--	--	--	--	1		3		1		1		2	
Anaemia	--	--	--	--	--	--	--	--	3	*	2	**	3	*	3	*	5	**
Musculoskeletal/Pain:																		
Arthralgia	0	***	1	***	4	*****	1	**	5	****	2	****	6	*****	9	****	1	***
Myalgia	0[b]	*b	<1[b]	*b	1	*	0	**	2	*	<1	**	1	**	10	***	0	**
Pain in extremity	--	--	--	--	<1	*	1	*	2	**	1	*	1	*	1	**	1	*
Pain	--	--	--	--	--	--	--	--	<1		0		0		4	*	1	
Musculoskeletal pain	--	--	--	--	--	--	--	--	<1	*	1		1	*	3	**	0	*

Table 21 (Continued)

Studies:	COMBI-d[b,524,603]				COMBI-v[412]				Co-BRIM[597]				COLUMBUS[606]			
Agent:	Dab		Dab/Tram		Vem		Dab/Tram		Vem		Vem/Cobi		Vem		Encor		Encor/Bini	
Grade:	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–4[c]	Any	3–4[c]	Any	3–4[c]	Any
Gastrointestinal:																		
Diarrhea	1	**	1	***	<1	****	1	***	1	***	7	******	2	***	2	*	3	****
Nausea	1	***	1	****	1	****	<1	***	1	***	1	****	2	***	4	****	2	****
Vomiting	1	*	1	***	1	**	1	***	1	*	2	***	1	**	5	***	2	***
Constipation	0[b]	*[b]	<1[b]	*[b]	<1	*	0	*	0	*	0	*	1	*	0	**	0	**
Cutaneous:																		
Rash	1	**	0	***	9	****	1	**	6	****	5	****	3	***	2	**	2	*
Pruritis	0[b]	*[b]	0[b]	*[b]	1	**	0	*	<1	**	1	**	0	*	1	**	1	*
Rash maculo-papular	--	--	--	--	--	--	--	--	5	**	7	**	4	*	1	*	0	
Rash generalized	--	--	--	--	--	--	--	--	1		<1		4	*	1	*	0	
Alopecia	0	***	1	*	<1	****	0	*	<1	***	<1	**	0	****	0	******	0	*
Dry skin	0[b]	*[b]	0[b]	*[b]	<1	**	0	*	0	**	1	**	0	**	0	***	0	**
Hyperkeratosis	1	****	0	*	1	**	0		2	***	<1	*	0	***	4	****	1	**
Keratosis pilaris	--	--	--	--	0	*	0		0	*	0		0	**	0	**	0	
Palmoplantar erythrodysesthesia syndrome	--	--	--	--	<1[d]	**[d]	0[d]	[d]	<1		0	*	1	*	14	*****	0	*
Palmoplantar keratoderma	1	**	1	*					0	*	0		1	**	2	***	0	*
Skin papilloma	0	**	0		1	**	0		<1	*	0	*	0	**	0	*	0	*
Photosensitivity reaction	0		0		<1	**	0		0	**	3	***	1	**	0		1	
Keratoacanthoma	1	*	2		--	--	--	--	9	*	1		3	*	0	*	1	
cSCC					<1		0		13	*	4		4	*	0		0	
Basal cell carcinoma	1	*	3		--	--	--	--	2		6	*	1		1		0	

--, data not reported; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; cSCC, cutaneous squamous cell carcinoma; GGT, gamma-glutamyl transferase.

[a] AE rates shown are for all AEs, regardless of whether or not they were treatment related. Table includes all AEs that occurred in >20% of patients or as high grade (grade 3–4 of 3–5) in >3% of patients in any arm in any of the four trials shown. Values are percent of patients who experienced at least one AE of any grade, grade 3–4 or grade 3–5. For the any grade column, 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. Blank indicates that <5% of patients experienced that AE.

[b] For AEs not reported in Long 2017,[603] data from Long 2014[524] are shown. COMBI-d data are from Long 2017[603] unless otherwise noted.

[c] In the COLUMBUS trial, toxicities leading to death were not recorded as CTCAE Grade 5 AEs, but instead were assigned grade 1 to 4 based on severity prior to death.

[d] In COMBI-v, palmar-plantar erythrodysesthesia, plantar-palmar hyperkeratosis, and palmoplantar keratoderma were reported as a combined term “hand-foot syndrome.”

Other Targeted Therapies: Imatinib

KIT mutations have been associated most commonly with mucosal and acral subtypes of melanoma.[22] Phase II studies testing imatinib or nilotinib, inhibitors of mutated KIT, in patients with *KIT*-mutated or *KIT*-amplified metastatic melanomas demonstrated 17% to 30% ORR and 35% to 57% disease control rate.[96-98,618-620] Unfortunately, most of these responses were of limited duration. These phase II studies included a significant portion of patients with non-cutaneous melanoma (29%–71% mucosal). The results show trends toward better response for patients with *KIT* mutations versus amplifications alone, and in some studies trends toward better response in mucosal melanoma compared with acral/CSD subtypes.[97,98,618] 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.[621,622]

Interleukin-2

High-dose IL-2 has been used extensively to treat metastatic melanoma in first-line and second-line settings. Although ORRs are modest (<20%), those who achieve a complete response (<10%) tend to have extremely durable responses and high rates of long-term survival.[623-627] Thus, although median OS is usually 11 to 12 months, approximately 10% of patients achieve long-term survival (>5 years).[623,625-629] 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).[623] Of the 12 patients with complete response, 10 survived at least 13 years. A retrospective comparative study found that response rate for high-dose IL-2 was higher among patients with prior ipilimumab treatment compared with patients with no prior immune checkpoint inhibitor therapy (ORR 21% vs. 12%).[630]

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.[631] 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,[632,633] temozolomide,[633] and paclitaxel with or without carboplatin.[634-638] These have demonstrated modest response rates less than 20% in first-line and second-line settings. Although early clinical trials suggested that nab-paclitaxel may provide higher response rates (22%–26% in phase II trials among chemotherapy-naïve patients with metastatic melanoma),[639,640] a phase III trial of patients with chemotherapy-naïve stage IV melanoma showed that nab-paclitaxel did not result in higher rates of response compared with dacarbazine (15% vs. 11%; $P = .239$).[641] This and other phase III randomized trials comparing chemotherapy regimens have failed to identify any regimens that provide both better response and OS relative to their counterparts.[633-635,641,642] A randomized phase III trial in patients with chemotherapy-naïve metastatic melanoma showed that selection of combination chemotherapy regimen based on an ex-vivo sensitivity assay did not improve response rate, PFS, or OS compared with dacarbazine monotherapy, but instead resulted in much higher rates of grade 3–4 AEs (40% vs. 12%; $P < .001$).[643]

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 and equivocal results from comparative phase III trials.[642,644]

Radiation Therapy for Extracranial Metastases

Palliative Radiation Therapy for Symptomatic Extracranial Metastases

Contrary to common perception that melanoma is radio-resistant, radiation often achieves palliation of symptomatic metastatic disease, including palliation of visceral, bone, and CNS metastases.[645-648] Clinically significant regression of radiated lesions of up to 60% has been reported in carefully selected patients.[649,650] A variety of treatment regimens are acceptable depending on location and/or clinical indication. Higher doses and/or hypofractionated regimens may be associated with more durable palliation.[646,648] Potential regimens with supporting citations can be found in the *Principles of Radiation Therapy for Melanoma* in the algorithm.[647,649,651,652]

Ablative Treatment for Extracranial Metastases

Higher doses utilizing conformal techniques such as stereotactic body radiation therapy (SBRT) may offer more durable local control and freedom from regional or distant progression.[653-655] SBRT may be used in selected patients with oligometastasis.[653] This potential benefit must be weighed against potential toxicities, and strict adherence to normal tissue constraints is recommended. Examples of dosing regimens for SBRT of the spine and for other body sites, along with supporting citations, are listed in the *Principles of Radiation Therapy for Melanoma* in the algorithm.

Radiation for Brain Metastases

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.[656-661] 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.[661,662] 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.[361,663-665] 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,[666-674] and a retrospective analysis by Hecht and colleagues[675] 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.[672-674] 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.[675] Acute dermatitis has also been reported in patients treated with WBRT and BRAF inhibitor therapy (either concurrent or sequential).[670,671] In the retrospective study by Hecht and colleagues,[675] 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[676] 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.[139,677-683] 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.[139,677,678,681,684] 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.[677,679,682,685] 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.[679,686-688]

NCCN Recommendations for Distant Metastatic Disease

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.

Recommendations for Limited Metastatic Disease

For limited metastatic disease, options include resection, if feasible, or systemic therapy. Observation is no longer a recommended option, even for patients with very limited stage IV disease, now that there are more effective active treatment options available. Systemic treatment should be followed by repeat scans to rule out the possibility that the disease is not more widespread, and to better select patients for surgical intervention.

Following systemic therapy, patients with resectable disease should be reassessed for surgery.

If completely resected, patients with no evidence of disease (NED) can be observed or offered adjuvant treatment. The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity. The recommended adjuvant treatment options are described in *Adjuvant Systemic Therapy for Melanoma*.

Patients with residual disease following incomplete resection for limited metastases should be treated as described below for disseminated disease.

Recommendations for Disseminated Disease

Disseminated disease can be managed by one or more of the following options, depending on the location of and extent of metastatic disease: clinical trial, systemic therapy, local treatment, or best supportive care (see the NCCN Guidelines for Palliative Care). For all systemic therapy options, consult the prescribing information for dosing recommendations. A number of options are available for systemic therapy, as described in the next two sections.

For extracranial metastases, local treatment options may include intralesional injection with T-VEC, resection, or radiation. T-VEC can be injected into nodal or distant metastases to help with disease control, but the impact on survival is not known. It may be useful for patients with very limited stage IV disease, or in combination with other treatment modalities. Symptomatic extracranial metastases can be managed with palliative resection and/or radiation. Radiation can be used for palliation of visceral, bone, and CNS metastases. Recommended techniques and dosing for different body sites, along with supporting citations, are listed in the *Principles of Radiation Therapy for Melanoma* in the algorithm.

For brain metastases, recommended localized treatment options and considerations for selecting systemic therapy are described in *Treatment of Patients with Brain Metastases.*

For patients considering multi-modality therapy for disseminated disease, interactions between radiation therapy and systemic therapies (eg, BRAF inhibitors, IFN alfa-2b, immune checkpoint inhibitors) need to be very carefully considered as there is potential for increased toxicity, particularly when utilizing higher doses of radiation. Because BRAF and/or MEK inhibitors may interact with radiation, consideration should be given to holding BRAF and/or MEK inhibitors ≥3 days before and after fractionated radiation therapy and ≥1 day before and after SRS (or other high-dose-per-fraction regimens).[689]

Except for patients rendered NED by surgery, all patients undergoing active treatment for distant metastatic disease should be regularly assessed for response or progression, both by clinical exam and imaging. Recommended imaging modalities are the same as for initial workup, as described in *General Guidelines for Imaging in Patients with Melanoma.*

Recommendations for Systemic Therapy

Recommendations for First-line Systemic Therapy

For first-line therapy of unresectable or distant metastatic disease, recommended treatment options include immune checkpoint inhibitors, BRAF-targeted therapy for patients with an activating *BRAF* V600 mutation, or clinical trial.

Immune checkpoint inhibitor options in this setting include anti-PD-1 monotherapy with pembrolizumab (category 1) or nivolumab (category 1) or nivolumab/ipilimumab combination therapy (category 1). Immune checkpoint inhibitors have been shown to be effective regardless of *BRAF* mutation status. The NCCN Panel considers all recommended immune checkpoint inhibitor options appropriate for both *BRAF* mutant and *BRAF* wild-type metastatic disease. The use of PD-L1 as a biomarker for selection of anti-PD-1 therapy and/or nivolumab/ipilimumab combination therapy is an emerging research issue with non-uniform application among the NCCN Member Institutions (category 2B). Descriptive analyses suggest that patients with low PD-L1 expression may benefit from nivolumab/ipilimumab combination therapy relative to nivolumab monotherapy. These analyses showed that patients with high PD-L1 expression may not benefit from addition of ipilimumab to nivolumab, and would do just as well on nivolumab monotherapy, and avoid the increased risk of toxicity associated with combination therapy.

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 to the 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 may improve PFS relative to nivolumab monotherapy, it is associated with a much higher risk of serious immune-mediated toxicities compared with nivolumab monotherapy. 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. Relative indications for combination nivolumab/ipilimumab in comparison to PD-1 monotherapy include: patient willingness to take on high risk of irAEs; absence of comorbidities or auto-immune processes that would elevate the risk of irAEs; patient social support and anticipated compliance with

medical team to handle toxicities; and absent/low tissue PD-L1 expression.

For patients with unresectable or distant metastatic disease harboring a *BRAF* V600-activating mutation, BRAF-targeted therapy first-line options include BRAF/MEK inhibitor combination therapy with dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib. All of these regimens are category 1 options based on results from phase 3 trials in the first-line setting (ie, COMBI-d, COMBI-v, CoBRIM, COLUMBUS). Although vemurafenib and dabrafenib are FDA approved as single-agent therapy for treatment of patients with distant metastatic or unresectable melanoma with *BRAF* V600E mutation,[397,398] these agents are almost never given without concomitant MEK inhibition. BRAF/MEK inhibitor combination therapy has been shown to have superior response rate, PFS, and OS compared with BRAF inhibitor monotherapy, as well as a similar or better toxicity profile, so the NCCN Panel recommends BRAF inhibitor monotherapy only in those rare cases where combination therapy is contraindicated. In such cases, BRAF inhibitor monotherapy remains a treatment option especially if the patient is not an appropriate candidate for immune checkpoint inhibitor therapy. Dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib combination therapy regimens are FDA approved for the treatment of patients with unresectable or distant metastatic melanoma with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test.[397-401,690] 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 the Clinical Laboratory Improvement Amendments (CLIA). Positive immunohistochemistry (IHC) staining of tumor for VE1 is sufficient for starting targeted therapy in patients who are symptomatic or have rapidly progressing disease. Due to risk of false positives and false negatives, all VE1 IHC results, both positive and negative, should be confirmed by sequencing. The NCCN Panel recommends that tissue for genetic analysis be obtained from either biopsy of a current metastasis (preferred) or from archival material. The NCCN Panel considers BRAF/MEK inhibitor combination therapy (or single-agent BRAF inhibitor therapy if combination therapy is contraindicated) as appropriate treatment options for metastatic disease with any type of activating *BRAF* V600 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,[399] 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.

For patients with documented *BRAF* V600 mutations, selection between first-line immune checkpoint inhibitors or 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, the presence or absence of cancer-related symptoms, and the patient's personal history of autoimmune disease or estimated risk (based on family history) of triggering autoimmunity by immunotherapy. Given that responses to immune checkpoint inhibitors 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. Other patients with asymptomatic metastatic melanoma may be good candidates for immune checkpoint inhibitor

therapy, 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 immune checkpoint inhibitor therapy; treatment selection should therefore be informed by consideration of the patient's overall health, medical history, concomitant therapies, comorbidities, and compliance.

When to Discontinue Treatment or Switch Systemic Therapy

Consistent with the FDA prescribing information, the NCCN Panel recommends discontinuing systemic therapy in cases of unacceptable toxicity. If there is residual disease at the time of discontinuation, it is recommended to switch to a different class of therapy. See *Guidelines for Therapy Selection in Previously Treated Patients.*

All patients undergoing systemic therapy for distant metastatic disease should be regularly assessed for response or progression, both by clinical exam and imaging. Recommended imaging modalities are the same as for initial workup, as described in *General Guidelines for Imaging in Patients with Melanoma*.

The NCCN Panel believes that a switch in systemic therapy is appropriate if there is confirmed disease progression during or after the course of systemic therapy. Additionally, for those treated with BRAF-targeted therapy who have achieved maximum clinical benefit (but not complete remission), a switch to immune checkpoint inhibitor therapy may be considered. Although there is no standard definition for maximum clinical benefit, it is commonly defined as no additional tumor regression on at least 2 consecutive scans taken at least 12 weeks apart. However, for patients on BRAF-targeted therapy with limited subsequent treatment options (ie, those who have already failed or are ineligible for immune checkpoint inhibitor therapy), it is not unreasonable to continue BRAF-targeted therapy beyond confirmation of partial response or stable disease, as changing to less effective treatments may result in disease progression. The optimal duration to administer BRAF-targeted therapy after achieving a durable complete response, partial response, or stable disease is not known.

For patients treated with immune checkpoint inhibitors, late responses or late improvements in response may occur. Some panel members may occasionally continue immune checkpoint inhibitor treatment beyond progression, as development of response after initial progression (sometimes referred to as "pseudo-progression") has been described. Therefore, in patients treated with immune checkpoint inhibitors it is recommended that progression be confirmed before deciding to switch to a different type of therapy. This is especially important in patients with limited options for subsequent therapy (ie, those who are *BRAF*-V600 wild-type). For patients who achieve complete response, partial response, or stable disease while on an immune checkpoint inhibitor, the optimal duration to administer therapy after achieving best clinical response remains unknown. Although exploratory analyses of prospective trials show high durability of responses long after discontinuation of immune checkpoint inhibitor therapy, there are no prospective randomized trial data comparing treatment for a defined duration versus ongoing treatment after best clinical response is achieved. Absent high-quality prospective data, there is a wide range of clinical practice.

Recommendations for Second-line or Subsequent Therapy

For patients with previously treated distant metastatic disease, data on the efficacy and safety of specific systemic therapies are in general less robust than data in the first-line setting. For a wide variety of agents there are prospective data demonstrating activity in previously treated patients, but prospective trials comparing these options are limited, and largely included patients whose previous therapies did not include the BRAF-targeted and immune checkpoint inhibitor options that are now preferred for first-line therapy. Interpretation of data from this setting is challenging because the patient population is highly heterogenous in terms of the

number and types of previous systemic therapies received, location and extent of metastatic disease, and speed of progression (symptomatic or not). Given the lack of high-quality data and the wide array of scenarios that present in the clinic, the NCCN Panel lists a large number of acceptable options for second-line or subsequent systemic therapy, with the general recommendation to consider therapies whose mechanism of action differs from prior lines of therapy that resulted in poor response or disease progression. The sections below first describe the rationale for including each of the options listed for second-line or subsequent systemic therapy, and then discuss recommendations for selecting among these options.

Options for Second-line or Subsequent Systemic Therapy

BRAF-Targeted Therapies and Immune Checkpoint Inhibitors

Based on the positive results from phase III trials supporting the recommended first-line therapies, the following immune checkpoint inhibitors and BRAF-targeted therapy regimens have been incorporated into the guidelines as options for second-line or subsequent systemic therapy for qualifying patients: nivolumab, pembrolizumab, nivolumab/ipilimumab combination, dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib 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 I/II trials in patients with previously treated advanced disease support second-line or subsequent systemic therapy for some of these options (eg, vemurafenib/cobimetinib, dabrafenib/trametinib, pembrolizumab). Use of nivolumab monotherapy in previously treated patients is supported by phase III trial data in this setting (Checkmate 037), although the results were less robust than those seen in the first-line setting. As in the first-line setting, BRAF inhibitor monotherapy is only recommended in the context of contraindications to BRAF/MEK inhibitor combination therapy; BRAF-targeted therapy (BRAF inhibitor monotherapy or BRAF/MEK inhibitor combination therapy) is only recommended for patients with *BRAF* V600-activating mutations, and there is no panel consensus on use of PD-L1 expression as a biomarker for selection of anti-PD-1 therapy (monotherapy or nivolumab/ipilimumab combination). See *Recommendations for First-line Systemic Therapy* for guidance on *BRAF* mutation testing.

Although the Checkmate 067 trial showed ipilimumab to have inferior response rate, PFS, and OS compared with nivolumab/ipilimumab combination and compared with nivolumab monotherapy, this trial included only patients with no previous systemic therapy for advanced disease. It is unclear whether the results would be the same in patients who had progressed on prior systemic therapy, particularly if previous lines of treatment included immune checkpoint inhibitors. For this reason, ipilimumab is included among the acceptable options for systemic therapy in previously treated patients. In addition, there are several prospective trials that demonstrated ipilimumab activity in patients with previously treated unresectable stage III/IV melanoma, although previous treatments did not include BRAF-targeted therapy or immune checkpoint inhibitors.

Interleukin-2

Although associated with significant risk of severe toxicity, IL-2 remains an option in the second-line or subsequent setting because it can provide long-term survival for the small percent of patients (<10%) with complete response.[623-627] Due to the low response rate and high toxicity, however, IL-2 is not a preferred option as it is considered less safe and less effective than immune checkpoint inhibitors or BRAF-targeted therapy options.

T-VEC ± Ipilimumab

Based on the results from a randomized phase II trial showing that intralesional T-VEC improved response rate in patients treated with systemic ipilimumab,[570] this combination is listed as an option for patients with injectable metastases. Because results of the trial did not demonstrate improved PFS or OS, ipilimumab/T-VEC combination therapy is a category 2B recommendation, only listed as an option for second or subsequent-line therapy (not first-line therapy), and is not a preferred option. Although anti-PD-1 therapy is generally preferred over ipilimumab, the NCCN Panel voted not to include combination therapy with T-VEC plus systemic anti-PD-1 therapy as a recommended option, both because there are insufficient randomized trial data on this specific combination, and because the effect of adding T-VEC to ipilimumab was fairly modest.

Imatinib

Activating *KIT* mutations are rare in patients with cutaneous melanoma, but for those who have them, imatinib may be helpful for disease control. Among patients with activating *KIT* mutations, fewer than half responded to imatinib, and randomized trials to assess impact on PFS and OS have not been conducted.[96-98] For these reasons imatinib is not listed as a preferred agent, even for patients with qualifying mutations, but may be useful for those who are ineligible for or unresponsive to more effective therapies (ie, immune checkpoint inhibitors, BRAF-targeted therapy).

Cytotoxic Therapy

Given that randomized trials have demonstrated that immune checkpoint inhibitors and BRAF-targeted regimens are all more effective than chemotherapy, cytotoxic therapy is not among the preferred options for systemic therapy, even in previously treated patients. For those who have failed or are ineligible for more effective options, however, cytotoxic therapy may be considered. Remarkable responses to cytotoxic therapies are occasionally observed, and these approaches can help with disease control or to reduce tumor load.

Best Supportive Care

Given the number of effective options to choose from, active treatment is appropriate for most patients. Best supportive care is usually reserved for those with very poor performance status, who have experienced progression despite multiple lines of therapy, and are ineligible for the preferred systemic treatment options.

Guidelines for Therapy Selection in Previously Treated Patients

Selection of second-line or subsequent systemic therapy remains a significant challenge due to the lack of prospective randomized comparisons in this setting and the fact that much of the data are from patients whose prior therapies did not include those currently recommended as first-line options (ie, BRAF/MEK inhibitor combination, anti-PD-1 monotherapy, ipilimumab/nivolumab combination therapy). As part of an NCCN initiative to provide guidance on treatment selection considering the evidence, relative efficacy, toxicity, and other factors that play into treatment selection, the NCCN Melanoma Panel has categorized all recommended systemic therapy regimens as “preferred,” “other recommended,” or “useful under certain circumstances.” For second-line or subsequent systemic therapy for advanced disease, preference stratification is particularly challenging because preference is highly dependent upon the details of each patient’s clinical history. Many case-specific factors should be considered when selecting second-line therapy, including response and toxicities on prior therapies, rate of progression of the underlying disease (symptomatic or not), presence or absence of CNS progression, the presence of symptoms, patient physiologic reserve, and patient preference and compliance.

In general, if a patient experienced progression of melanoma during or shortly after a systemic therapy, re-challenge with the same therapy or therapy of the same class is unlikely to yield a response and is not recommended. The exception to this rule is that for patients who progressed on single-agent immune checkpoint inhibitor therapy,

nivolumab/ipilimumab combination therapy is a reasonable treatment option. In addition, although anti-CTLA-4 (ipilimumab) and anti-PD-1 (ie, nivolumab, pembrolizumab) agents are both immune checkpoint inhibitors, they are not considered the same class of agent because they target different molecules. Therefore, for patients who previously received ipilimumab, subsequent treatment with anti-PD-1 therapy is a recommended option, and vice versa. Given that for both immune checkpoint inhibitors and BRAF-targeted therapy there are data showing responses upon rechallenge, the NCCN Panel recommends that, for patients who experience disease control (complete response, partial response, or stable disease) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered.

Immune Checkpoint Inhibitor Administration

For all systemic therapy options, consult the prescribing information for dosing recommendations.

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 22% of patients receiving anti-PD-1 therapy, 20% to 30% of patients receiving ipilimumab monotherapy, and in 50% to 60% of patients receiving 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 immune checkpoint inhibitors.

Close monitoring of potentially lethal irAEs in patients receiving immune checkpoint inhibitors is essential. 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. Recommendations for monitoring and management immune-related toxicities associated with immune checkpoint inhibitors are summarized in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities. There are two broad categories of irAE monitoring and management: one for ipilimumab-containing regimens and one for anti-PD-1 monotherapy. 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 NCCN Guidelines for Management of Immunotherapy-Related Toxicities[691] and the relevant package inserts[394-396]; 2) other FDA-approved materials with detailed descriptions of the signs and symptoms of irAEs associated with ipilimumab and detailed protocols for management[692]; and 3) standard institutional protocols for monitoring and managing irAEs, with multidisciplinary input among various specialists as warranted.

Prevention and Management of BRAF Inhibitor Toxicities

Fever is common in patients receiving BRAF-targeted therapy, and is often episodic, with onset often 2 to 4 weeks following the start of therapy. Pyrexia may be associated with chills, night sweats, rash, dehydration, electrolyte abnormalities, and hypotension. Pyrexia should be managed by treatment discontinuation and use of anti-pyretics such as acetaminophen and/or NSAIDs. Stopping or holding BRAF/MEK inhibitor therapy at the onset of pyrexia will often interrupt the episode. After resolution of fever and pyrexia-related symptoms, resumption of BRAF/MEK inhibitor treatment at reduced dose may be tried. Upon re-exposure, repeat pyrexia events can occur. Patients treated with BRAF-targeted therapy should

also be educated to report joint pain and swelling, visual changes, and cutaneous manifestations. Patients who develop skin complications should be promptly referred to a dermatologist for management and monitoring. Patients should be advised about the possibility of photosensitivity associated with these agents, and counseled to minimize UV exposure, wear UV-protective clothing, and use high-SPF sunblock.

BRAF and/or MEK inhibitors may interact with radiation and can lead to increased CNS, pulmonary, dermatologic, and visceral toxicity. Consideration should be given to holding BRAF and/or MEK inhibitors ≥3 days before and after fractionated RT and ≥1 day before and after SRS (or other high-dose per fraction regimens).

Management of Interleukin-2 Toxicities

Caution is warranted in the administration of high-dose IL-2 due to the high degree of toxicity reported. If IL-2 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.

Recommendations for 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.[693-695]

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.[696-702] Imaging tests detected 7% to 49% of recurrences.[126,696,698-702] 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.[696,698,700-702] Even in prospective trials where laboratory tests were conducted regularly, detection of recurrence by blood work results was extremely rare.[126,700]

Recurrences detected by patients or physician clinical exams are usually local, regional satellite or in-transit, or nodal, and less commonly distant.[126,700] Recurrences detected by imaging, on the other hand, are more likely distant and nodal; local or in-transit recurrences are rarely detected by imaging.[126,700] These findings, combined with the low percentage of recurrences identified by imaging some studies,[696,698,701,702] 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.[693,694,703-709] 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.[694,695,710]

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.[126,697,700,711,712] 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).[243,244,246,713]

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.[711,712] 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.[126,697,698,700,712] Studies indicate that the risk of recurrence plateaus at between 2% to 5%.[126,697,714,715] Late recurrence (more than 10 years after diagnosis) is well documented, especially for patients initially presenting with early-stage melanoma.[714-716] 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.[697] 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.[700] For patients initially presenting with stage III disease, the risk of recurrence reached low levels after only 2.7 years.[700] 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.[126,712] 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.[712]

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.[697,700,717-720] The risk of developing a second primary melanoma generally decreases with time from diagnosis of the first primary melanoma.[721] 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,[717] and about half are diagnosed within the first year.[718] 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).[718] Second primary melanomas are likely

to occur at the same body region as the original lesion,[720] and are usually thinner than the original lesion,[718,722] 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.[718,722]

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.[722-724]

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. [711,715,725-727] Survival nodal or distant metastatic recurrences also depend on the diameter of largest metastasis, number of metastases, and presence of visceral metastases.[711,726]

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.[728] 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.[723] 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.[729,730] There is increasing evidence that regular sunscreen use may diminish the incidence of subsequent melanoma.[731] 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).[732] 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 complete response 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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