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Target Audience: This activity is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Release date: April 10, 2021; Expiration date: April 10, 2022

Learning Objectives:

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

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

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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To view all of the conflicts of interest for the NCCN Guidelines panel, go to [NCCN.org/disclosures/guidelinepanelisting.aspx](https://www.nccn.org/disclosures/guidelinepanelisting.aspx).

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Melanoma: Cutaneous, Version 2.2021

Featured Updates to the NCCN Guidelines

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ABSTRACT

Over the past few years, the NCCN Guidelines for Melanoma: Cutaneous have been expanded to include pathways for treatment of microscopic satellitosis (added in v2.2020), and the following Principles sections: Molecular Testing (added in v2.2019), Systemic Therapy Considerations (added in v2.2020), and Brain Metastases Management (added in v3.2020). The v1.2021 update included additional modifications of these sections and notable revisions to Principles of: Pathology, Surgical Margins for Wide Excision of Primary Melanoma, Sentinel Lymph Node Biopsy, Completion/Therapeutic Lymph Node Dissection, and Radiation Therapy. These NCCN Guidelines Insights discuss the important changes to pathology and surgery recommendations, as well as additions to systemic therapy options for patients with advanced disease.

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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
 - [Gross description of lesion, including presence of macroscopic satellite lesions in the gross tumor specimen](#).
 - [Dermal mitotic rate per mm²](#)^f
 - [Lymphovascular/angiolymphatic invasion](#)^d
 - [Growth phase](#)
 - [Histologic subtype \(if desmoplastic, specify pure or mixed^g\)](#)
 - [Tumor-infiltrating lymphocytes \(TILs\)](#)
 - [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

^aInternational 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

^bCollege 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

^cMicrosatellitosis 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).

^dAt 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.

^eFor 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}

^fDermal 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.

^gIn 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.

^hSee Principles of Molecular Testing (ME-C).

ME-B
2 OF 3

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Overview

In 2021, an estimated 106,110 individuals will be diagnosed with cutaneous melanoma in the United States and about 7,180 will die of metastatic melanoma.¹ The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma: Cutaneous includes recommendations for biopsy of pigmented lesions suspected to be cutaneous melanoma, and workup, treatment, and follow-up recommendations for patients with pathologically confirmed lesions. These guidelines cover management of all stages of cutaneous melanoma, from melanoma in situ (MIS) through stage IV disease, including recurrent disease. They do not address noncutaneous melanoma, such as uveal and mucosal types, which differ significantly in presentation, genetic profiles, staging, patterns of progression, and response to treatment.²⁻⁴

Overview of Staging and Treatment of Cutaneous Melanoma

Cutaneous melanomas are categorized as follows: localized disease with no evidence of regional or distant metastases (stages 0–II), regional nodal/in-transit disease (stage III), and distant metastatic disease (stage IV). Primary treatment of most newly-diagnosed melanomas includes wide excision (WE) of the primary melanoma, sentinel lymph

node biopsy (SLNB) for pathologic staging in appropriate patients with eligible tumor thickness, and additional treatment of regional or distant metastatic disease if present. For patients with resected stage III–IV melanoma, adjuvant systemic immune and targeted therapies are an important means of improving disease-free survival.

Revisions to Pathology Recommendations

Patients presenting with a suspicious pigmented skin lesion should undergo a biopsy to establish a definitive diagnosis of cutaneous melanoma; complete/excisional biopsy is preferred to maximize histopathologic exam and microstaging of the primary tumor. Complete biopsy should be performed with narrow (1–3 mm margins) around the concerning lesion and may be full thickness (eg, fusiform/elliptical, disk, or punch techniques) or involve shave removal into the deep reticular dermis via the saucerization technique.⁵ Breslow depth of the initial biopsy, along with other histologic factors (ulceration, high mitotic rate, lymphovascular invasion) is used to determine whether SLNB is warranted in clinically node-negative patients, with the caveat that SLNB should optimally be performed at the time of WE. Importantly, both primary tumor thickness and ulceration status are incorporated across the AJCC staging manual 8th edition (AJCC-8) stage

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.

^aFor 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.

^bExcision 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.

ME-E
1 OF 2

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III categories.⁶ In recent updates to the NCCN Guidelines for Melanoma: Cutaneous, the recommendations for elements to be included in the pathology report have been revised to more closely reflect those listed as key factors in national and international dermatopathology guidelines, as illustrated in supplemental eTable 1 (available with this article at JNCCN.org).⁵⁻⁸ In addition, the description of some of these pathology report elements and guidance for how to measure and record them have been modified in recent updates to the NCCN Guidelines, as described in greater detail subsequently.

Mitotic Rate

Dermal mitotic rate measures the proportion of cells undergoing mitosis and is an indicator of tumor proliferation. The AJCC-8 recommends recording mitotic rate (using the “hot spot” technique to determine the number of mitosis per mm²), since it remains an independent prognostic factor for melanoma specific survival (MSS) across all thickness categories.⁶ For instance, a mitotic rate ≥11/mm² reduces 5-year MSS of patients with node-negative T1–T4 melanoma to 84%.⁹ The NCCN panel has systematically reviewed the many studies that evaluated the relationship between primary tumor mitotic rate in

T1 melanoma and likelihood of SLN positivity in patients and noted that whereas results varied across studies that compared presence/absence of mitosis or used low mitotic index cutoff values,¹⁰⁻²⁸ studies consistently found that mitotic index >2/mm² was significantly associated with a higher risk of SLN positivity in thin melanoma.²⁹⁻³⁷ As such, the NCCN Guidelines have been updated to reflect that for T1a lesions (Breslow depth <0.8 mm, nonulcerated), mitotic index >2/mm² is one of several adverse features that may increase the risk of nodal metastasis and should be considered when discussing SLNB as part of the primary workup (ME-2, footnote 1, available at NCCN.org).

Satellite Lesions: Microscopic and Macroscopic

Lymphatic metastasis within or adjacent to the melanoma biopsy site or subsequent WE scar are termed satellite metastasis, whereas those located between the primary tumor and the regional lymph node basin are termed in-transit metastasis. Both confer a stage III diagnosis, as do microsatellites,^{6,38,39} which are observed histopathologically in either the biopsy or WE specimen.^{6,9} An analysis of the AJCC-8 worldwide database that included patients with and without synchronous regional nodal disease showed that survival outcomes were similar for patients

with microsatellites, macroscopic satellites, and in-transit metastases, with all 3 conferring worse survival.⁹ Other studies corroborate that the presence of microsatellites, clinical satellites or in-transit metastasis are associated with poorer outcomes (relapse-free survival [RFS], disease-specific survival [DSS], and overall survival [OS]), even among patients with synchronous nodal disease.^{36,40–44} Evidence of microsatellites, clinical satellites, and in-transit metastases is a critical element of initial workup and should be included in pathology reports on biopsy or WE specimens, as should any macroscopic satellites on the gross tumor specimen (ME-B, 2 of 3, page 366).

In AJCC-8, the presence of microsatellites, clinical satellites or in-transit metastasis upstages patients with and without regional nodal disease,⁶ resulting in an N (node) classification of N1c, N2c, or N3c based on the number of tumor-involved regional lymph nodes (0, 1 or ≥ 2 , respectively; see AJCC Staging Tables, ST-2 and ST-4, in these guidelines, at NCCN.org).

In patients with clinical stage I/II melanoma, the presence of microsatellites has also been linked to higher rates of SLN positivity,^{10,20,44,45} and a positive SLNB upstages a patient to at least N2c, stage IIIC.^{9,46–48} For these reasons the NCCN Guidelines recommendations for workup and management of patients with microsatellites (ME-4), clinical satellites, or in-transit disease (ME-7) differ from those for patients without regional disease (ME-1 and ME-2) or who have regional disease limited to lymph nodes (ME-5 and ME-6; all pages available in these guidelines at NCCN.org).

In contrast to the findings from the analysis of the AJCC-8 database, several studies across various subpopulations reported higher MSS rates for patients with stage III melanoma based on microsatellitosis alone,^{47,48} compared with those with satellite/in-transit metastasis^{46,49} or those with a positive SLNB.^{9,50} In addition, patients with stage III melanoma based on the presence of microsatellites alone (without regional nodal disease) were not included in the prospective randomized trials testing adjuvant therapy for resected stage III cutaneous melanoma.^{51–55} For these reasons, the NCCN Guidelines recommendations for adjuvant treatment consideration differ for those with stage III based on microsatellitosis (ME-4) versus those with stage III based on nodal or clinical satellite/in-transit disease (ME-5 through ME-7; available at NCCN.org).

Lymphovascular/Angiolymphatic Invasion

Lymphovascular invasion (LVI) refers to the presence of melanoma cells within the lumina of blood vessels (termed vascular invasion) or lymphatics (termed lymphatic invasion), or both.^{6–8} None of the analyses of the AJCC staging database identified LVI as a significant prognostic factor for survival,^{9,56,57} although results from other studies varied.^{22,42,43,58–65} A number of studies have found

LVI to be an independent predictor of SLN positivity,^{15,23,28,36,47,63,66} so it is listed as one of the adverse features to be considered when discussing SLNB as part of the primary workup for patients with Stage I, T1a disease (ME-2, footnote 1, available at NCCN.org). CAP and ICCR include LVI as a core element, the AJCC encourages reporting, and the AAD Guidelines list it as an optional element to report. The NCCN Guidelines encourage consistent synoptic reporting of LVI or angiolymphatic invasion (ME-B 2 of 3, page 366).

Regression

In some cases the primary tumor may show signs of regression, a process in which the host immune system has recognized and destroyed all or part of the tumor.^{6,8} The prognostic relevance of this feature is controversial, with some studies showing no correlation between regression and outcomes (SLN status, disease-free survival [DFS], recurrence, metastasis, survival), other studies showing regression to be associated with poor prognosis (DFS, metastasis, survival), and still others showing regression associated with favorable outcomes (lower SLN positivity and improved DFS and MSS).^{67,68}

The NCCN Guidelines encourage reporting of regression if it is extensive ($>75\%$) or extending beneath the measured Breslow thickness (ME-B 2 of 3, page 366). The presence of regression could impact accurate measurement of Breslow thickness, so in some cases surgeons may take it into account when deciding on WE margins or whether to perform SLNB (eg, on tumors <0.8 mm thick), although there are no published data to support this approach.

Other Histologic Features of Importance

Some studies suggest that neurotropism (perineural invasion) may increase the chance for local recurrence in the setting of “pure” desmoplastic melanoma.^{69,70} The NCCN Guidelines encourages reporting of neurotropism, noting that extensive neurotropism is one of the risk factors for local recurrence in desmoplastic melanoma used to identify cases where adjuvant radiation may be considered, along with head and neck location, and/or close histologic margins (category 2B; ME-H 1 of 7, footnote b; available at NCCN.org).

Although CAP still lists tumor infiltrating lymphocytes as a core element for cutaneous melanoma excision specimens,⁷ it is a noncore or nonessential element in other guidelines (supplemental eTable 1).^{5,6,8} In v1.2021, the NCCN panel removed tumor infiltrating lymphocytes from the list of features encouraged for reporting due to concerns about reproducibility and lack of prognostic value.

Studies that have included vertical growth phase as a variable have produced very mixed results regarding its association with LN metastasis^{29,30,32,71} and other outcomes,

with most studies finding that it is not an independent prognostic for RFS or survival.^{62,72–75} Likewise, the NCCN panel removed vertical growth phase from the list of reportable features, as this variable does not appear to have independent prognostic value or impact management decisions.

Histologic Subtype

Traditional clinicopathologic growth patterns (ie, superficial spreading, nodular, lentigo maligna and acral lentiginous) have evolved according to the site of origin (epithelium- versus non-epithelium-derived), role of cumulative sun damage (CSD; high-, low-, or non-CSD-related), and frequency of *BRAF*, *NRAS*, and other oncogenic mutations.⁷⁶ These melanoma subtypes have been incorporated into the 2018 WHO classification of skin tumors⁷⁷ to denote differences in terms of molecular drivers, pathogenesis, and natural history. The prognostic value of histologic subtype is controversial, with varying results across studies.^{10,37,42,46,47,62,63,73,74,78–87} The AJCC staging system and much of the data informing management is primarily based on the common superficial spreading and nodular subtypes, so consideration of alternative management approaches may be appropriate for patients with less common subtypes. For example, lentigo maligna melanoma may be associated with subclinical peripheral extension beyond visible margins, so may require wider surgical margins or alternative surgical approaches and tissue processing to clear histologically.^{88,89}

Desmoplastic melanoma is characterized by malignant spindle cells separated by prominent fibrocollagenous or mixed fibromyxoid stroma.^{6,8} “Pure” desmoplastic melanoma is defined as desmoplastic component occupying >90% of a dermal invasive tumor. Mixed desmoplasia defined by typical features of desmoplastic melanoma (desmoplastic component) mixed with densely cellular tumor foci without fibrosis and desmoplasia (nondesmoplastic component), with desmoplastic melanoma areas occupying 10%–90% of the invasive melanoma.⁹⁰ In v1.2021, the NCCN Guidelines were updated to include the definition of pure desmoplastic melanoma as >90% of invasive melanoma associated with prominent stromal fibrosis.

Compared with mixed desmoplasia or other melanoma subtypes, studies consistently show that “pure” desmoplastic melanoma is associated with improved DSS, and a lower likelihood of nodal metastasis (including lower rates of SLN positivity).^{81,90–101} However, due to variability across studies in the rate of SLN positivity,^{69,81,91,93–104} the role of SLNB in patients with pure desmoplastic melanoma remains controversial. Although adjuvant radiation to the primary melanoma site is generally not recommended due to low risk of recurrence after adequate WE, some desmoplastic melanomas are at increased risk of local recurrence,

and adjuvant radiation to the primary site may be considered, as noted above (category 2B).

Histologic Margin Status

Histologic margin status in the biopsy and WE specimens (to include whether the peripheral and deep margin are involved/positive or uninvolved/negative) is a key element for reporting among pathology guidelines (supplemental eTable 1). Consistent with CAP,⁷ ICCR,⁸ and AAD,⁵ the NCCN Guidelines recommend recording whether in situ and/or invasive melanoma is present at the peripheral and/or deep margins on the biopsy or excision specimen. For histologically negative margins on the WE 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 (see “WE for Invasive Cutaneous Melanoma,” page 370). However, narrow pathologic margins (particularly of the invasive component) are associated with higher risk of local recurrence, and this information may warrant consideration of further surgical resection (ME-E, page 367).

Management of Primary Melanoma

WE Management of Melanoma In Situ: Lentigo Maligna or Acral Lentiginous Subtypes

For both in situ and invasive primary melanoma, WE is the primary treatment, although no randomized trials have assessed surgical margins for MIS, and those assessing surgical margins for invasive cutaneous melanoma mostly included patients with superficial spreading or nodular melanoma subtypes (supplemental eTable 2). Management of 2 subtypes of MIS—lentigo maligna (LM) and acral lentiginous type—present surgical challenges because of subclinical extension of tumor cells, location in anatomically constrained sites (eg, face, palms, soles), in addition to the presence of atypical/actinic melanocytic hyperplasia in the LM subtype (high-CSD melanoma) which often confounds histologic assessment of margin status.^{88,105–117} For this reason, surgery with complete circumferential peripheral and deep margin assessment (CCPDMA) has been studied in MIS to improve histologic clearance and decrease the chance of local recurrence (typically persistent disease-type, with in situ and/or radial growth phase).^{88,89,109,111,112,115,118–131} Mohs micrographic surgery (MMS) and staged excision with formalin-fixed, paraffin-embedded (ie, permanent) sections are types of CCPDMA, though these techniques have not yet been prospectively studied in comparison with conventional WE for MIS or invasive CM for local control. The NCCN Guidelines were updated to clarify that for MIS, LM and acral lentiginous types, surgical margins >0.5 cm may be needed and techniques for

comprehensive histologic margin assessment may be considered. Published data also suggest a role for CCPDMA in LM with a minimally invasive (T1a) component,^{132,133} as reflected on ME-E (page 367). For MIS, identification of an invasive component in the central debulking specimen is not uncommon, so the NCCN Guidelines have been updated to indicate that if MMS is performed, permanent section analysis should be performed to provide complete pathologic staging.^{88,124}

WE for Invasive Cutaneous Melanoma

Although much if not all of the melanoma may have been removed by the initial biopsy, WE provides a wider and deeper excision to prevent local recurrence. Multiple prospective randomized trials have been conducted in an effort to define optimal peripheral surgical margins for WE of primary invasive (but not in situ) melanoma (supplemental eTable 2) and have demonstrated that WE with sufficient margins results in very high rates of local control (>96%). These prospective randomized trials are considered category 1 level of evidence for the NCCN recommendations regarding clinical (peripheral) margin extent for WE of primary invasive melanoma, as shown on ME-E (page 367). These trials defined clinical margins as the distance between the incision and the grossly visible edge of the tumor, as measured by the surgeon at the time of surgery. The NCCN Guidelines excision recommendations regarding peripheral margin size are therefore based on clinical margins taken at the time of surgery, not gross or histologic margins measured by the pathologist (ME-E, footnote b).

Concerns have been raised regarding the applicability of these randomized controlled trial (RCT) results across all melanomas, since these trials included mainly superficial and nodular melanoma subtypes on the trunk and extremities and very few patients with lesions on the head or neck (supplemental eTable 2) or other anatomic locations where wide margins would not be possible (ie, acral sites). Large retrospective analyses have attempted to evaluate the relationship between margin size and outcomes using patient populations that include patients with invasive primary melanoma on the head and neck.^{83,85,87,134–139} Of those that evaluated surgical margins,^{85,134–138} multivariable analyses showed that the width of clinical margins (1 vs 2 cm for melanomas 1–2 mm thick,^{137,138} or 2–4 mm thick,⁸⁵ or 1–4 mm thick¹³⁴) did not impact local/intransit RFS, overall RFS, DFS, or MSS. In studies that evaluated histopathologic excision margins (minimum distance between the surgical edge and the invasive component of the melanoma), multivariable analyses sometimes found that narrower peripheral histologic margins were associated with increased risk of local recurrence, locoregional recurrence, and overall DFS, but results were not entirely consistent across studies.^{83,85,87,138} Results from multivariable analyses more

consistently showed that peripheral histopathologic margins were not correlated with MSS or OS.^{83,85,138} Based on these analyses, the NCCN Guidelines were updated to clarify that although peripheral resection margins may be modified to accommodate individual anatomic or functional considerations, narrower than recommended margins may increase the risk for local recurrence (ME-E, bullet 1, page 367), and footnote language has been added to indicate that narrower peripheral histologic margins have been associated with higher rates of local recurrence for invasive melanoma, though not worse MSS.^{83,85,87,138}

Evidence relating narrower margins to outcomes is based on retrospective studies, and the NCCN Guidelines have been updated to note that the safety and efficacy of narrower surgical margins has not been evaluated through prospective randomized trials. At least one large retrospective analysis found that narrower than recommended surgical margins is associated with increased likelihood of positive or equivocal histopathologic margins,¹⁴⁰ although predicting histopathologic margin width based on surgical margins is not entirely straightforward.¹⁴¹ The NCCN Guidelines have been updated to caution that narrower than recommended surgical margins may increase the likelihood of margin positivity and local recurrence, and may warrant further surgical resection.

Due to the challenges of obtaining the recommended WE margins in sites with anatomic or functional constraints and the local recurrence risk if narrower surgical margins are used, surgical techniques and processing to provide comprehensive pathologic assessment prior to surgical repair have been investigated, including MMS and staged excision with permanent sections.^{109,111,119,120,125,133,142–145} However, while there are multiple prospective randomized trials supporting conventional WE with the recommended margins (supplemental eTable 2), there have been no prospective comparisons of different excision methods, including conventional WE, MMS, and staged excision with permanent sections. Available retrospective studies in invasive melanoma suggest that MMS or staged excision may result in similar low recurrence rates as conventional WE,^{119,120,143,144,146,147} but prospective, randomized trial data are needed for confirmation. The NCCN Guidelines have been updated to clarify that MMS is not recommended for primary treatment of invasive cutaneous melanoma. However, because the RCTs supporting WE largely excluded patients with lesions in anatomically constrained areas, and there are no high-quality data to inform surgical method for lesions in these areas, the NCCN Guidelines have been updated to indicate that MMS may be considered selectively for MIS (LM and acral lentiginous types) and for minimally invasive (T1a) LM melanoma in anatomically constrained areas, along with other surgical methods that provide comprehensive histologic assessment, such as staged excision with permanent sections for dermatopathology review.

Sentinel Lymph Node Biopsy

Cutaneous melanoma typically presents with a clinically localized primary lesion.¹ Most regional nodal melanoma presents microscopically (ie, clinically occult) and is detected via SLNB.^{9,50} Patients with a positive SLNB are at higher risk of recurrence and may now be followed with nodal basin ultrasound surveillance (where radiologic expertise is available) without completion lymph node dissection, given lack of improved MSS in 2 RCTs assessing the merits of completion lymph node dissection following a positive SLNB vs clinical observation with nodal ultrasound.^{148–150} Although SLNB is considered minimally invasive, it is not without risks of complications. In general, if a patient's risk of a positive SLN is <5% (ie, T1a melanoma), NCCN does not recommend SLNB; if a patient's risk of a positive SLN is 5%–10% (ie, T1b melanoma), NCCN recommends discussing and considering SLNB; and if the probability of a positive SLN is >10% (T2a–T4b melanoma), NCCN recommends that SLNB should be discussed and offered. NCCN panel considerations regarding SLNB, including information from initial biopsy of the primary lesion that is used to determine appropriateness of SLNB are summarized in supplemental eTable 3 and should take into account patient age, functional status, and life expectancy. The use of prognostic gene expression profiling (GEP) tests (before or after SLNB) requires further investigation across large, prospectively-enrolled cohorts of unselected patients. Given the low probability of metastasis in stage I melanoma and a higher proportion of false-positive results,^{151–154} the NCCN panel concluded that currently available GEP tests should not replace pathologic staging procedures, be used to determine SLNB eligibility, or guide clinical-decision making in this subset of patients (see ME-2A, footnote d, and ME-F 1 of 3; available in these guidelines at NCCN.org). Principles of nuclear medicine, surgery, and pathology pertaining to SLNB have also been recently revised (ME-F 2 and 3; available in these guidelines at NCCN.org).

Treatment of Unresectable Stage III or Distant Metastatic Disease (Stage IV): Updates to Systemic Therapy Options

Anti-PD-1/Anti-CTLA-4 Combinations

For several years, combination therapy with nivolumab/ipilimumab has been a recommended option for first-line or second- or subsequent-line systemic therapy for unresectable or distant metastatic disease, based on the results from Checkmate-067 and Checkmate-069 (supplemental eTable 4). These trials both used nivolumab 1 mg/kg (NIVO1) plus ipilimumab 3 mg/kg dosing (IPI3), which is associated with a high rates of grade 3–4 treatment-related adverse events (TRAEs) as shown in supplemental eTable 4. Investigators have explored new combinations of anti-PD-1 and anti-CTLA-4 in an attempt to reduce the rate of grade 3–5 toxicity while preserving the antitumor

efficacy of combination therapy. One such approach is the use of “full dose” anti-PD-1 (eg, nivolumab 3 mg/kg [NIVO3]) in combination with a lower dose of anti-CTLA-4 (eg, ipilimumab 1 mg/kg [IPI1]). The randomized double-blind Checkmate 511 trial showed that this approach (NIVO3/IPI1) significantly reduced the rate of high-grade TRAEs compared with NIVO1/IPI3 (supplemental eTable 4; $P=.006$ for grade 3–5 TRAEs). Based on these results, the NCCN Guidelines now indicate that while NIVO1/IPI3 is an FDA approved regimen,¹⁵⁵ NIVO3/IPI1 is associated with lower rates of immune-related toxicity, although longer follow-up is needed to determine equivalence of therapeutic efficacy between the 2 dosing regimens (ME-J 1 of 4, available in these guidelines at NCCN.org).

Several trials are exploring “full dose” pembrolizumab (2 mg/kg or 200 mg) in combination with lower-dose ipilimumab (IPI1) for patients with unresectable or distant metastatic disease (supplemental eTable 4). Like the trials testing nivolumab/ipilimumab, these trials included an option for single-agent anti-PD-1 therapy after the 4 doses of combination therapy. The phase IB open label trial (KEYNOTE-029) showed that in patients with advanced melanoma, and no prior checkpoint immunotherapy, pembrolizumab combined with low-dose ipilimumab resulted in a high response rate, long duration of response (84% of responses lasted at least 36 months), and long PFS and OS (supplemental eTable 4). These results appear to be on par with results from similar patient populations treated with nivolumab/ipilimumab combination in randomized trials (supplemental eTable 4, see results from Checkmate 067 and Checkmate 069). The rate of grade 3–4 TRAEs (47%) is similar to or lower than that seen for NIVO1/IPI3 across trials (range, 48%–59%; but higher than that seen for NIVO/IPI1 [33%] in Checkmate 511 [supplemental eTable 4]). Because KEYNOTE-029 is a single-arm study, the NCCN panel voted to include pembrolizumab/low-dose ipilimumab in the first-line setting as an “other recommended regimen”, category 2B (ME-I, 1 of 8; available at NCCN.org).

Another single-arm trial (NCT02743819, phase II) tested pembrolizumab/low-dose ipilimumab in patients with advanced melanoma and recent progression on an anti-PD-1 agent and no prior ipilimumab treatment (supplemental eTable 4). In an analysis of 70 patients (67 evaluable for response), 31% responded, with a median PFS of 4.7 months and 21% of patients experiencing a grade 3–4 TRAE (supplemental eTable 4). The NCCN panel voted to include this combination as a category 2A preferred option for patients who have progressed on prior anti-PD-1 therapy (ME-I, 1 of 8; available in these guidelines at NCCN.org).

BRAF/MEK Inhibitors Plus Checkpoint Immunotherapy Triplet Combinations

For patients with unresectable or distant metastatic disease harboring a *BRAF* V600-activating mutation,

selection between first-line immune checkpoint inhibitors or BRAF/MEK inhibitor therapy can be difficult given the lack of comparative phase II/III clinical trials. The advantage of BRAF/MEK inhibitor therapy is high response rates (65%–70%; see supplemental eTable 5), and relatively rapid time to response (reflects time to first tumor response assessment: 6 weeks in BRIM-7, 8 weeks in other trials).^{156–159} Although the median duration of response to BRAF/MEK inhibitor therapy is in the range of 12.0 to 18.6 months (supplemental eTable 5), there have been concerns dating back to the era of BRAF monotherapy, when response durations were much shorter, that targeted therapy may not elicit immunologic memory required for durable antitumor responses. For anti-PD-1–based immune checkpoint inhibitor therapy, response rates in trials are between 35%–40% for single-agent therapy and around 60% for anti-PD-1/ipilimumab combination therapy (see supplemental eTable 4). Responses to immune checkpoint inhibitors can take time to develop in some patients, with late responses observed over a year after starting treatment, and initial partial responses that may convert to complete responses after long-term follow-up (see trials in supplemental eTable 4). Responses to immune checkpoint inhibitors appear to be highly durable in this setting, with large trials reporting median duration of response for anti-PD-1 containing regimens ranging from 22 months to several years (supplemental eTable 4).

Several trials are currently assessing whether the high likelihood of response seen with BRAF/MEK inhibitor therapy and the durability of response seen with immune checkpoint inhibitors can both be achieved in patients with activating *BRAF* V600 mutations. Results have recently been reported from a number of randomized phase II-III trials testing triplet combinations of BRAF, MEK and a PD-1 (eg, pembrolizumab, spartalizumab) or PD-L1 inhibitors (eg, atezolizumab) as first-line systemic therapy for unresectable stage III or stage IV cutaneous melanoma (supplemental eTable 6). These trials found that the triplet combinations did not improve response rate compared with BRAF/MEK inhibitor doublets. However, the triplet combinations did improve the duration of response compared with the doublets (supplemental eTable 6, footnote d). In both IMspire150 and KEYNOTE-022, the triplet combination improved PFS, although in KEYNOTE-022 this

was not apparent in the prespecified analysis after 9.5 months follow-up (supplemental eTable 6). COMBI-I showed a nonsignificant trend toward improved PFS with the triplet regimen compared with BRAF/MEK inhibition alone. In all 3 trials, there was no clear benefit in OS, although longer follow-up may be needed. Until mature OS data are published, it is therefore not clear that triplet regimens are preferred over sequential BRAF/MEK inhibitor therapy followed by immune checkpoint inhibitor therapy (or the converse order). Whereas KEYNOTE-022 and COMBI-I both show higher rates of grade 3–5 TRAEs with the triplet versus the doublet regimen, IMspire150 showed similarly high rates of grade 3–4 TRAEs across arms (supplemental eTable 6), but reported more immune-mediated AEs in the triplet versus doublet arms (63% vs 51%). IMspire150 showed similar rates of discontinuation due to TRAEs across arms. The NCCN panel voted to include both triplet regimens as “other recommended” first-line systemic therapy options for patients with metastatic or unresectable cutaneous melanoma who have a *BRAF* V600-activating mutation, with vemurafenib/cobimetinib/atezolizumab as category 2A and dabrafenib/trametinib/pembrolizumab as category 2B.

Summary and Conclusions

Advances in melanoma diagnosis, prognosis, and therapy will continue with ongoing investigation of various molecular techniques (eg, GEP and circulating tumor DNA [ctDNA] assays) to more accurately define the risk of relapse. Prospective investigation is required using large contemporary data sets and compared with optimized phenotypic models to support use of molecular tests for SLNB eligibility, therapeutic decisions regarding adjuvant therapy, indications for imaging surveillance, and intensity of patient follow-up. Ongoing investigation of sequential and combination regimens of targeted and immune therapy, including novel agents, holds promise in prolonging survival in patients with advanced disease.

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Supplemental online content for:

Melanoma: Cutaneous, Version 2.2021

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eTable 1: Pathology Report Elements: Comparisons With Other Guidelines

eTable 2: Studies that Evaluated Surgical Margins of Wide Excision of Invasive Cutaneous Localized Primary Melanoma

eTable 3: Impact of Initial Workup and Biopsy on Staging and NCCN SLNB Recommendations

eTable 4: Anti-PD-1 Monotherapy and Combinations with Ipilimumab in Advanced Melanoma

eTable 5: BRAF/MEK Inhibitor Combination in Advanced Melanoma: Phase III Randomized Trial

eTable 6: BRAF/MEK Inhibitors Plus Checkpoint Immunotherapy Triplet Combinations in Advanced Melanoma: Randomized Trials

eTable 1. Pathology Report Elements: Comparisons With Other Guidelines

Element	NCCN v2020	NCCN v2.2021	AJCC Staging, 8th Edition, 2017 ¹	CAP Excision Specimen Report, 4.2.0.0, 2020 ^{a,2}	ICCR Reporting Guide, 2019 ³	AAD Guidelines, 2019 ⁴
Breslow thickness	Mandatory element	Mandatory element	Required for T stage	Required (invasive only)	Core element	Essential
Ulceration	Mandatory element	Mandatory element	Required for T stage	Required (invasive only) Optional: extent ulceration	Core element (status); noncore (extent)	Essential
Microsatellites	Report	Report ^b	Required for N stage	Required (invasive only)	Core element	Essential
Macroscopic satellite lesions in gross tumor specimen	Encourage reporting	Encourage reporting	Required for N stage	Required (invasive only)	Core element	Strongly recommended (clinical)
Dermal mitotic rate, per mm ²	Encourage reporting	Encourage reporting	Report	Required (invasive only)	Core element	Essential
LVI/Angiolymphatic invasion	Encourage reporting	Encourage reporting	Report	Required (invasive only)	Core element	Optional
Histologic subtype	Encourage reporting	Encourage reporting		Required		Optional
Desmoplastic (pure or mixed)	Encourage reporting	Encourage reporting ^c		Optional	Core element	
Regression	Encourage reporting	Encourage reporting ^d	Report	Required	Noncore element	Optional
Neurotropism/PNI	Encourage reporting	Encourage reporting	Report	Required (invasive only)	Core element	Optional
Anatomic level of invasion (Clark level)			Report	Optional (invasive only)	Noncore element	Optional
Vertical growth phase	Encourage reporting					Optional
TILs	Encourage reporting		Report	Optional (invasive only)	Noncore	Optional
Peripheral margin status	Report	Report ^e		Status required; extent and location optional ^f	Core element	Essential
Deep margin status	Report	Report ^e		Status required; extent optional ^f	Core element	Essential

Mandatory element = minimal element to be reported.

Encourage reporting = encourage consistent synoptic reporting.

For AJCC, "report" = additional factors recommended for clinical care.

Abbreviations: AAD, American Academy of Dermatology; AJCC, American Joint Committee on Cancer; CAP, College of American Pathologists; ICCR, International Collaboration on Cancer Reporting; LVI, lymphovascular invasion; PNI, perineural invasion; TILs, tumor infiltrating lymphocytes.

^aCAP protocol for excision specimens lists core data elements, conditional data elements, and optional data elements. It states that for accreditation purposes, only the definitive primary cancer resection specimen is required to have the core and conditional data elements reported in a synoptic format. This table shows which elements are required for accreditation versus optional.

^bIn v1.2021, description of microsatellitosis was changed to remove minimal tumor nest diameter and minimal width of normal tissue between primary lesion and satellite.

^cIn v1.2021, description was changed to include definition of pure desmoplastic melanoma as >90% of invasive melanoma associated with prominent stromal fibrosis.

^dIn v1.2021, added description to "regression": "(if extensive [>75%] or extending beneath measured Breslow thickness)."

^eIn v1.2021, description was changed to no longer require reporting of extent and location for positive margins.

^fCAP protocol lists peripheral and deep margin status (negative/present for invasive/in situ) as required, but measurement of distance of in situ or invasive melanoma from the closest peripheral or deep margin is optional.

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eTable 2. Studies that Evaluated Surgical Margins of Wide Excision of Invasive Cutaneous Localized Primary Melanoma

Study Publications	Enrollment (Years)	N	MIS, LMM, ALM n (%)	Site: Trunk, Limb, Head/Neck (%)	Tumor Thickness (mm)	Peripheral Margin (cm)	Follow-Up (y)	RFS or DFS, HR [95% CI]; P Value ^a	OS	MSS or DSS, HR [95% CI]; P Value ^a
WHO Melanoma Program Veronesi et al, 1998 ¹ ; Veronesi & Cascinelli, 1991 ²	1980–1985	612	17 (3%), not reported ^b	39%, 61%, 0 ^b	≤2	1 vs ≥3	8	DFS: NS	NS	Not reported
Swedish Melanoma Study Group Cohn-Cedermark, 2000 ³	1982–1991	989	1 (<1%), 4 (<1%), 6 (<1%) ^c	55%, 42%, <1% ^c	>0.8–2.0	2 vs 5	8 (LR) 11	RFS: NS	NS	NS
Intergroup Melanoma Surgical Trial, Group A Balch et al, 1993 ⁴ ; Balch et al, 2001 ⁵	1983–1989	468	Excluded ^d	39%, 52%, 9% ^d	1–4	2 vs 4	10	LR: NS	Not reported	NS
France Khayat et al, 2003 ⁶	1981–2000	326	1 (<1%), excluded ^e	29%, 63%, 5% ^e	≤2	2 vs 5	16	DFS: NS	NS	Not reported
UK ^f Thomas et al, 2004 ⁷	1993–2001	900	Not reported ^g	45%, 54%, 0 ^g	>2	1 vs 3	5.7	LRR (MV): 1.34 [1.06–1.70]; P=.02 RFS (MV): 1.25 [1.02–1.55]; P=.03 ^h	NS	NS
Hayes et al, 2016 ⁸							8.8	Not reported	NS	1.24 [1.01–1.53]; P=.041 ^h
Swedish and Danish Melanoma Study Groups NCT01183936: Gillgren et al, 2011 ⁹	1992–2004	936	Not reported, 9 (1%), 2 (<1%) ⁱ	60%, 39%, 0 ⁱ	>2	2 vs 4	6.7	LR: NS RFS: NS	NS	NS
NCT03638492: Utjes et al, 2019 ¹⁰							19.6	Not reported	NS	NS

Abbreviations: ALM, acral lentiginous melanoma; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; LMM, lentigo maligna melanoma; LR, local recurrence; LRR, locoregional recurrence (local, in-transit, or nodal); MIS, melanoma in situ; MSS, melanoma-specific survival; MV, multivariate analysis; NS, nonsignificant; OS, overall survival; RFS, recurrence-free survival (any type of recurrence).

^aHR and P value are only provided when the difference between arms was statistically significant.

^bIn the WHO study, 17 patients with Clark level I melanoma (MIS by definition) were included in the analysis. Histologic subtype was not reported. The study excluded patients with lesions on the face, fingers, or toes. The study did not report whether any of the patients had lesions elsewhere on the hands or feet. 16 patients with primary melanoma located on the head or neck were not evaluated.

^cThe Swedish Melanoma Study Group trial entry criteria required *malignant* melanoma measuring >0.8 to ≤2.0 mm in thickness, yet reported that 1 patient had melanoma in situ. The trial entry criteria included patients with lesions on the trunk or extremities (except hands and feet), but reported that among the randomized patients, 9 (<1%) had tumors located on the head-neck, and 3 on the hand, and 4 on the foot. All analyses were performed separately for all randomized patients as well as for all eligible patients, leading to identical conclusions.

^dIn the Intergroup trial, entry criteria required stage I/II melanoma, per the AJCC staging criteria at the time, so it is presumed that MIS was excluded. LMM and DM were excluded. No other subtypes were mentioned in the report. Eligibility criteria required that melanoma location allow for excision with the assigned margin. Lesion location was reported as proximal extremity in 24% and distal extremity in 28% of patients.

^eIn the French trial, 86% had superficial spreading, 13% nodular, and <1% listed as no class or missing. One patient (<1%) had a lesion with Clark level I, which by definition is MIS. The trial excluded patients with lesions arising from melanosis, lentigo, and acral. The trial excluded patients with melanoma on the toe, nail, or finger. Site was reported as "other" for 1.5% of patients.

^fUnited Kingdom Melanoma Study Group, British Association of Plastic Surgeons, Scottish Cancer Therapy Network, and the Clinical Trials and Statistics Unit at the Institute of Cancer Research, Sutton, United Kingdom.

^gThe UK trial enrolled patients with *malignant* melanoma with thickness ≥2 mm, so it is unlikely that any patients in this trial had MIS. Histologic subtype was not reported. The trial included 31% of patients with lesions on a distal limb, 23% on a proximal limb; patients with lesions on the palms of hand or soles of feet were excluded. Site information was missing for 1% of patients. Patients with melanomas on the head or neck were excluded.

^hHR for DFS is based on multivariate analysis. Analysis after a median follow-up of 5.7 years showed no significant difference in OS or MSS, but analysis after a median follow-up of 8.8 years showed significantly better MSS 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 OS (unadjusted HR, 1.14 [95% CI, 0.96–1.36]; P=.14).

ⁱIn the Swedish and Danish Melanoma Study Group trial, patients were required to have melanoma >2 mm in thickness, and there were no patients with Clark level I reported, so it is unlikely that any MIS lesions were included. Although melanomas on the hands, feet, head, and neck were meant to be excluded, there were 2 patients with lesions on the neck (<1%) and on the sole (<1%). The 2 patients with neck lesions were excluded from the analysis of OS and RFS based on margin of excision.

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eTable 3. Impact of Initial Workup and Biopsy on Staging and NCCN SLNB Recommendations ^a						
Results of Initial Workup and Biopsy of Primary			AJCC Clinical Stage After Biopsy of Primary Lesion ^{a,1}			NCCN SLNB Recommendation ^b
Breslow Thickness	Ulceration	Satellites	T	N	Overall	
N/A	Present or absent	N/A	Tis: MIS ^c	N0	Stage 0	SLNB generally not recommended unless uncertainty about adequacy of microstaging ^{d,e}
<0.8 mm	Absent	ND	T1a	N0	Stage IA	If no other adverse features, SLNB generally not recommended unless uncertainty about adequacy of microstaging ^{d,e} . If adverse features present, discuss and consider SLNB ^{e,f,g,h,i}
<0.8 mm	Present	ND	T1b	N0	Stage IB	Discuss and consider SLNB ^{e,f,g,h,i}
0.8–1.0 mm	Absent or present	ND	T1b		Stage IB	Discuss and consider SLNB ^{e,f,g,h,i}
>1.0–2.0 mm	Absent	ND	T2a	N0	Stage IB	Discuss and offer SLNB ^{e,h,i,j}
>1.0–2.0 mm	Present	ND	T2b	N0	Stage IIA	Discuss and offer SLNB ^{e,h,i,j}
>2.0–4.0 mm	Absent	ND	T3a	N0	Stage IIA	Discuss and offer SLNB ^{e,h,i,j}
>2.0–4.0 mm	Present	ND	T3b	N0	Stage IIB	Discuss and offer SLNB ^{e,h,i,j}
>4.0 mm	Absent	ND	T4a	N0	Stage IIB	Discuss and offer SLNB ^{e,h,i,j}
>4.0 mm	Present	ND	T4b	N0	Stage IIC	Discuss and offer SLNB ^{e,h,i,j}
≤4.0 mm	Absent or present	Micro	T1a–T4a	≥N1c	Stage IIIB/C	Discuss and offer SLNB ^{i,j,k}
>4.0 mm	Absent or present	Micro	T4b	≥N1c	Stage IIID	Discuss and offer SLNB ^{i,j,k}

Abbreviations: Macro, macroscopic satellites present; micro, microscopic satellites present; MIS, melanoma in situ; N/A, not applicable; ND, not detected; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy

^aThis table only covers patients without clinically apparent nodal, satellite, or in-transit metastases and without evidence of distant metastatic disease (clinical M0).

^bNCCN recommendations are category 2A unless otherwise noted.

^cMIS is defined as lesions with melanoma cells restricted to the epidermis and associated adnexal structures.¹

^dIf a patient's risk of a positive 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).

^eIn patients with pure desmoplastic melanoma (>90% of invasive melanoma associated with prominent stromal fibrosis), SLN positivity is less common compared with 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.

^fIf 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/mm² [particularly in the setting of young age], lymphovascular invasion, combination of these factors).

^gDecision not to perform SLNB may be based on significant patient comorbidities, patient preference, or other factors.

^hSLNB is an important staging tool. Although 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 and overall survival in selected high-risk patients with stage III disease.

ⁱSLNs should be evaluated with serial sectioning and immunohistochemistry.

^jDecision not to perform SLNB may be based on significant patient comorbidities, patient preference, or other factors (such as advanced patient age).

^kMicrosatellitosis, 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 IIC. SLNB should be considered in patients with microsatellitosis, especially if it will alter management decisions.

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eTable 4. Anti-PD-1 Monotherapy and Combinations with Ipilimumab in Advanced Melanoma^a

Trial			Patients			Efficacy Results ^c				
Name and References	Phase Design	Median Follow-Up (mo)	Tx Naïve	CNS Mets ^b	Treatment Arms	Response Rate	Median DoR (mo)	Median PFS (mo)	Median OS (mo)	Grade 3/4 TRAEs ^d
Randomized Trials										
CheckMate 037 NCT01721746 ^{1,2}	III R, OL	~24	0 ^e	20%	Nivo 3 mg/kg q2wk (n=272)	27%	31.9	3.1 ^f	15.7	14%
				14%	Chemo (n=133)	10%	12.8	3.7	14.4	34%
CheckMate 066 NCT01721772 ^{3,4}	III RDB	38 ^g	100%	3.6%	Nivo 3 mg/kg q2wk (n=210)	43%*	NR (>38)	5.1*	37.5*	15%
		39 ^g		DTIC (n=208)	14%	6	2.2	11.2	18%	
KEYNOTE-006 NCT01866319 ⁵⁻⁷	III R, OL	57.7	34% ^h	9%	Pembro 10 mg/kg q2wk (n=279)	37% ^{i,**}	53.5	8.4**	32.7*	17%
					Pembro 10 mg/kg q3wk (n=277)	36%**				17%
					Ipi 3 mg/kg q3wk x 4 doses (n=278)	13%	NR (>21)	3.4	15.9	20%
CheckMate 067 NCT01844505 ⁸⁻¹¹	III RDB	54.6	100%	3.6%	Nivo 1 mg/kg + ipi 3 mg/kg, both q3wk x 4 doses; then nivo 3 mg/kg q2wk (n=314)	58% ^{j,**}	50.1	11.5 ^{i***}	NR ^{i,**}	59%
		36.0			Nivo 3 mg/kg q2wk (n=316)	45%**	NR (>50)	6.9**	36.9**	23%
		18.6			Ipi 3 mg/kg q3wk x 4 doses (n=315)	19%	14.4	2.9	19.9	28%
CheckMate 069 NCT01927419 ^{12,13}	II RDB	25	100%	3%	Nivo 1 mg/kg + ipi 3 mg/kg, both q3wk x 4 doses; then nivo 3 mg/kg q2wk (n=95)	59%**	NR	ND**	NR	54%
					Ipi 3 mg/kg q3wk x 4 doses (n=47)	11%	NR (>7)	3.0	NR	20%
CheckMate 511 NCT02714218 ¹⁴	IIIb/IV RDB	18.8	100%	2.2%	Nivo 3 mg/kg + ipi 1 mg/kg, both q3wk x 4 doses; then nivo 480 mg q4wk (n=180)	46%	NR	9.9	NR	33%
		18.6		2.8%	Nivo 1 mg/kg + ipi 3 mg/kg, both q3wk x 4 doses; then nivo 480 mg q4wk (n=180)	51%	NR	8.9	NR	48%
Trials Supporting Pembrolizumab + Low-Dose Ipilimumab										
KEYNOTE-029 NCT02089685 ^{15,16}	IB OL	36.8	87%	5.9%	Pembro 2 mg/kg (later amended to 200 mg) + ipi 1 mg/kg, both q3wk x 4 doses; then pembro 2 mg/kg q3wk (n=153)	62%	NR	NR ^k	NR ^k	47%
NCT02743819 ^{17,18}	II OL	Not reported	0 ^l	Not reported	Pembro 200 mg + ipi 1 mg/kg, both q3wk x 4 doses; then pembro 200 mg q3wk (n=70)	31%	Not reported	4.7	Not reported	21%

Abbreviations: AE, adverse event; chemo, Investigator's choice chemotherapy of single-agent dacarbazine or carboplatin/paclitaxel combination; CNS, central nervous system; CNS mets, percent of patients with central nervous system metastases at baseline; DoR, duration of response; DTIC, dacarbazine; HR, hazard ratio; ipi, ipilimumab; ND, not determined (Kaplan-Meier curve plateaus above 50%); nivo, nivolumab; NR, not reached (further follow-up needed); OL, open label; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; R, randomized; RDB, randomized, double-blind; Tx naïve, percent of patients with no prior treatment of unresectable or metastatic disease; TRAE, treatment-related adverse event.

^aUnresectable stage III or IV melanoma.

^bPatients with active CNS metastases were excluded from the trials. For all studies except CheckMate 067 and KEYNOTE-029, the percentage of patients with a history of brain metastases is shown. For CheckMate 067 and KEYNOTE-029, the percentage of patient with brain metastases at baseline is shown.

^cResponse rate is the percentage of patients that achieved complete or partial response. Median PFS and OS were determined using the Kaplan-Meier method. For randomized trials, significant difference compared with the control arm is denoted by * ($P < .001$) and ** ($P < .0001$).

^dPercent of patients who experienced any type of treatment-related AE of grade 3 or 4.

^eEntry 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.

^fIn the CheckMate 037 trial, PFS was not significantly different between arms (HR, 1.03; 95% CI, 0.78–1.436).

^gMedian follow-up for CheckMate 066 was not reported, but minimum follow-up was 39 months in each arm.

^hIn KEYNOTE-006, patients could have had up to one prior systemic therapy, but patients previously treated with checkpoint inhibitors were excluded.

ⁱIn KEYNOTE-006, comparison of the pembrolizumab q2wk and q3wk arms showed no difference in overall response rate ($P = .82$), PFS ($P = .62$), or OS ($P = .93$).

^jIn 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).

^kIn KEYNOTE-029, median PFS and OS was not reached after median follow-up of 36.8 months; PFS and OS rate at 36 months, 59% and 73.4%.

^lIn NCT02743819, patients were required to have progressed on anti-PD-1 therapy immediately prior, but were not allowed to have prior anti-CTLA-4 treatment.

* $P < .001$ compared with the control arm.

** $P < .0001$ compared with the control arm.

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eTable 5. BRAF/MEK Inhibitor Combination in Advanced Melanoma^a: Phase III Randomized Trials

Trial		Patients				Efficacy Results ^b									AEs Grade 3/4 ^c
Name and References	Phase Design	Median Follow-Up (mo)	Prior BRAFi	Tx Naïve	Brain Mets	Treatment Arms	Response Rate	Median DoR (mo)	Median PFS (mo)	Median OS (mo)	HR	P	HR	P	
COMBI-d ^{1,2} NCT01584648	III RDB	20	0	100%	Not reported ^e	Dab + tram (n=211)	69% ^f	12.0	11.0	25.1	0.75	.0014	0.75	.0107	48% ^g
		16	0			Dab + pbo (n=212)	53%	10.6	8.8	18.7					50% ^g
COMBI-v ³ NCT01597908	III R, OL	11	0	100%	Not reported ^e	Dab + tram (n=352)	64%	13.8	11.4	NR		<.001		.005	52%
		10	0			Vem (n=352)	51%	7.5	7.3	17.2					63%
Co-BRIM ⁴⁻⁶ NCT01689519	III RDB	14.2; 18.5 ^j	0	100%	<1% ^e	Vem + cob (n=247)	70%	13.0	12.3	22.3		<.0001		.005	75%
			0		<1% ^e	Vem + pbo (n=248)	50%	9.2	7.2	17.4					61%
COLUMBUS ⁷⁻⁹ NCT01909453	III R, OL	48.8	0	70% ^k	5% ^e	Encor + bini (n=192)	64%	18.6	14.9	33.6		<.0001 ^l		<.0001 ^l	68%
			0	70% ^k	Not reported ^e	Encor (n=194)	52%	15.2	9.6	23.5		.0038 ^l		.033 ^l	68%
			0	70% ^k	2% ^e	Vem (n=191)	41%	12.3	7.3	16.9					66%

Abbreviations: AE, adverse event; bini, binimetinib; BRAFi, BRAF inhibitor; brain mets, percent of patients with brain metastases at baseline; cob, cobimetinib; dab, dabrafenib; DoR, duration of response; encor, encorafenib; HR, hazard ratio; NR, not reached; OL, open label; OS, overall survival; Pbo, placebo; PFS, progression-free survival; R, randomized; RDB, randomized double-blind; tram, trametinib; Tx naïve, percent of patients with no prior treatment of unresectable or distant metastatic disease; vem, vemurafenib.

^aUnresectable (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.

^bResponse 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.

^cPercent of patients with grade 3/4 AEs of any cause (treatment or otherwise).

^dBRIM-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.

^ePatients with active brain metastases were excluded from the trial. Treated stable brain metastases were allowed.

^fIn 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.

^gJohnson 2014¹⁰ reported results from 2 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.

^hIn 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.

ⁱBased on analysis after ≥36-month follow-up for all living patients.

^jCo-BRIM median follow-up shown for response and PFS analysis; OS and safety analysis.

^kIn COLUMBUS, 30% of patients in each arm had prior systemic immunotherapy, mostly interferon or interleukins. Other types of prior systemic therapy were not allowed.

^lIn 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).

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eTable 6. BRAF/MEK Inhibitors Plus Checkpoint Immunotherapy Triplet Combinations in Advanced Melanoma^a: Randomized Trials

Trial		Patients			Efficacy Results ^c							Grade 3–5 TRAEs ^d
Name and References	Phase Design	Median Follow-Up (mo)	Tx Naïve	CNS Mets ^b	Treatment Arms	ORR	Median DoR (mo)	Median PFS (mo)	Median OS (mo)			
IMspire150 NCT02908672 ¹	III RDB	18.9	100%	2%	Atezo + vem + cobimetinib (n=256) ^e	66% NS	21.0	15.1	HR, 0.78 (95% CI, 0.63–0.97); P=.025	2-y: 60% ^f	NS	79% ^g
				3%	Pbo + vem + cobimetinib (n=258) ^e	65%	12.6	10.6		53% ^f		73% ^g
KEYNOTE-022 NCT02130466 ²	II RDB	36.6	100%	1.7%	Pembro + dab + tram (n=60)	63% NS	25.1 ^h	16.9	HR, 0.53 (95% CI, 0.34–0.83) ⁱ	NR	HR, 0.64 (95% CI, 0.38–1.06); NS	58% ^j
					Pbo + dab + tram (n=60)	72%	12.1	10.7		26.3		25%
COMBI-I NCT02967692 ³	III RDB	27.2	100%	Not reported	Sparta + dab + tram (n=267)	69% NS	NR	16.2	HR, 0.82 (95% CI, 0.66–1.03); P=.042; NS	NR	HR, 0.785	55%
				Not reported	Pbo + dab + tram (n=265)	64%	20.7	12.0		NR		33%

Abbreviations: AE, adverse event; atezo, atezolizumab (anti-PD-L1 agent); CNS, central nervous system; CNS mets, percent of patients with central nervous system metastases at baseline; cobimetinib (MEK inhibitor); dab, dabrafenib (BRAF inhibitor); DoR, duration of response; HR, hazard ratio; NE, not estimable; NR, not reached (longer follow-up needed); NS, not statistically significant; ORR, overall response rate; OS, overall survival; Pbo, placebo; pembro, pembrolizumab (anti-PD-1); PFS, progression-free survival; RDB, randomized, double-blind; sparta, spartalizumab (anti-PD-L1 agent); TRAE, treatment-related adverse event; tram, trametinib (MEK inhibitor); Tx naïve, percent of patients with no prior systemic treatment of unresectable or distant metastatic disease; vem, vemurafenib (BRAF inhibitor).

^aUnresectable stage III or stage IV melanoma, with a BRAF V600 mutation.

^bPatients with active CNS metastases were excluded from the trials.

^cResponse 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.

^dPercent of patients who experienced any type of TRAE of grade 3–5.

^eIn IMspire150, the first cycle included only vemurafenib plus cobimetinib; atezolizumab or placebo were used in cycle 2 onward.

^fIn IMspire150, further follow-up is needed to determine median OS. 2-year OS rates were reported, and thus far there were no significant differences in OS.

^gIn IM-spire150, rates reported in the table are for grade 3/4 TRAEs. 2 patients in the test arm and 1 patient in the control arm died of treatment-related AEs.¹

^hIn KEYNOTE-022, although ORR did not differ significantly between arms, median duration of response was significantly longer for the triplet versus doublet: HR, 0.32 (95% CI, 0.17–0.59).²

ⁱIn KEYNOTE-022, prespecified analysis after 9.5 months of follow-up showed median PFS of 16.0 months vs 10.3 months, with *P*=.043, did not reach the planned benefit for a statistically significant improvement.⁴

^jIn KEYNOTE-022, one patient in the triplet arm died of treatment-related pneumonitis.² No other grade 5 TRAEs were reported.

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