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Commentary

Clinicopathological Features, Staging, and Current Approaches to Treatment in High-Risk Resectable Melanoma

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Abstract

The incidence of melanoma in the United States has been increasing over the past several decades. Prognosis largely depends on disease stage, with 5-year melanoma-specific survival ranging from as high as 99% in patients with stage I disease to less than 10% for some patients with stage IV (distant metastatic) disease. Fortunately, in the last 5–10 years, there have been remarkable treatment advances for patients with high-risk resectable melanoma, including approval of targeted and immune checkpoint blockade therapies. In addition, results of recent clinical trials have confirmed the importance of sentinel lymph node biopsy and continue to refine the approach to regional lymph node basin management. Lastly, the melanoma staging system was revised in the eighth edition *AJCC Cancer Staging Manual*, which was implemented on January 1, 2018. Here we discuss these changes and the clinicopathological features that confer high risk for locoregional and distant disease relapse and poor survival. Implications regarding the management of melanoma in the metastatic and adjuvant settings are discussed, as are future directions for neoadjuvant therapies.

Melanoma incidence in the United States has risen over the past several decades (1). Most patients with stages I–II cutaneous melanoma have a favorable, albeit heterogeneous prognosis; those with stages III–IV melanoma have a historically poorer prognosis. In the past 5–10 years, the clinical landscape for patients with stages III–IV melanoma has markedly improved with the introduction of more effective systemic therapies, including molecularly targeted agents and immune checkpoint blockade (ICB) (2–11) in the adjuvant and metastatic arenas, resulting in notable improvements in survival. Surgical management also continues to evolve, with confirmation of the importance of sentinel lymph node (SLN) biopsy (SLNB), refinement of our approach to completion lymph node dissection (CLND) (12–14), and the development of neoadjuvant treatment strategies. Thus, prognostic features affecting recurrence risk and outcomes across the continuum of stages II–IV melanoma must be considered during clinical decision-making with respect to nodal staging, adjuvant therapy, and neoadjuvant therapy protocols. Here, we discuss the evolving landscape of high-risk melanoma, including staging, clinical features, and contemporary and future directions in the multidisciplinary management of patients with stages II–IV resectable melanoma.

Melanoma Staging

AJCC Eighth Edition Melanoma Staging System

The American Joint Committee on Cancer (AJCC) Melanoma Expert Panel (MEP) revised the melanoma staging system, published in the eighth edition (8e) *AJCC Cancer Staging Manual* (15) in 2017 (Figure 1). Revisions (Table 1) were based on analyses from the International Melanoma Database and Discovery Platform, containing prospective data for over than 46 000 patients with stages I–III melanoma diagnosed between 1998 and 2014 (16). Additional input was obtained from the legacy AJCC seventh edition (7e) stage IV analysis, supplemented by published clinical trial data (16).

Primary Melanoma Clinicopathological Features

Breslow (tumor) thickness has been validated in multiple studies, including recent AJCC analyses (Figure 2A), and continues to represent a foundational component of melanoma staging (16–22). Previous studies have suggested that survival among T1 category patients is related to tumor thickness, with a possible clinically important "breakpoint" of 0.7–0.8 mm (18,19,21).

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N Category	Tumor-involved regional lymph nodes, No.	Presence of in-transit, satellite, and/or microsatellite metastases	T Category								
			T0 No evidence of primary tumor	T1a <0.8 mm without ulceration	T1b <0.8 mm with ulceration or 0.8–1.0 mm with or without ulceration	T2a >1.0–2.0 mm without ulceration	T2b >1.0–2.0 mm with ulceration	T3a >2.0–4.0 mm without ulceration	T3b >2.0–4.0 mm with ulceration	T4a >4.0 mm without ulceration	T4b >4.0 mm with ulceration
N0	No regional metastases detected	No	—	IA	IA	IB	IIA	IIA	IIB	IIB	IIC
N1a	1 clinically occult (ie, detected by SLN biopsy)	No	—	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N1b	1 clinically detected	No	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N1c	No regional lymph node disease	Yes	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2a	2 or 3 clinically occult (ie, detected by SLN biopsy)	No	—	IIIA	IIIA	IIIA	IIIB	IIIB	IIIC	IIIC	IIIC
N2b	2 or 3, at least 1 of which was clinically detected	No	IIIC	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC
N2c	1 clinically occult or clinically detected	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC
N3a	≥4 clinically occult (ie, detected by SLN biopsy)	No	—	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3b	≥4, at least 1 of which was clinically detected, or presence of any number of matted nodes	No	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID
N3c	≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIIC	IIID

Figure 1. AJCC 8th edition pathological prognostic groups (TNM) for stage I to III cutaneous melanoma*†. NX = Regional nodes not assessed (eg, SLN biopsy not performed, regional nodes previously removed for another reason); SLN = sentinel lymph node; T0 = no evidence of primary tumor (eg, unknown primary or completely regressed melanoma); Tis = melanoma in situ; TX = thickness cannot be assessed. Exception: pathological N category is not required for T1 melanomas, use cN. *Pathological stage is IV for any T, any N, and M1 disease. †Adapted and used with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original and primary source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017), published by Springer International Publishing (Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin AB, Edge SB, Greene, FL, et al. eds. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer; 2017:563–585).

Table 1. Summary of major changes in the AJCC 8e Melanoma Staging System*

Change	Summary of change
Definition of primary tumor (T)	1) Primary melanoma thickness and ulceration continue to define T category strata. Tumor thickness is measured to the nearest 0.1 mm, not the nearest 0.01 mm. (eg, melanomas measured as 0.75 to 0.84 are reported as 0.8 mm). 2) The definitions of T1a and T1b have been revised. T1a melanomas include those <0.8 mm without ulceration while T1b melanomas include those 0.8–1 mm with or without ulceration and those <0.8 mm with ulceration. 3) Mitotic rate is no longer a T1 category criterion but should be documented for all invasive primary melanomas.
Definition of regional lymph node (N)	1) The number of metastasis-containing regional lymph nodes remains an N-category criterion. 2) The presence or absence of nonnodal regional metastases (ie, microsatellites, satellites, or in-transit metastases) are categorized in the N-category criterion based on the number (if any) of tumor-involved regional lymph nodes. 3) Sentinel node tumor burden is a regional disease prognostic factor that should be collected for all patients with positive sentinel nodes but is not used to determine N-category groupings.
Definition of distant metastasis (M)	1) Anatomic site of distant metastatic disease remains the primary component of the M category. M1a is defined by nonvisceral (distant cutaneous, subcutaneous, nodal) metastasis, M1b by lung metastasis, and M1c by non-CNS metastasis. A new M1d designation is added to include distant metastasis to the CNS with or without any other distant sites of disease. M1c no longer includes CNS metastasis. 2) Elevated LDH level no longer defines M1c. LDH remains an important predictor of survival in stage IV and is designated as "0" for "not elevated" and "1" for "elevated" for all sites of distant disease [lung metastasis with elevated LDH is M1b (1), not M1c].
AJCC prognostic stage groups	1) No overall change in T subcategories. Definitions of stages IA and IB are refined. 2) Stage III groupings have been redefined based on multivariable models to include both T-category and N-category elements. 3) Stage III has increased from three to four subgroups, with the addition of a stage IIID subgroup, with heterogeneous outcomes across subgroups. 4) Stage IV is not further substaged (ie, M1c is stage IV, not stage IVc).

*Adapted (with permission of the American Joint Committee on Cancer [AJCC], Chicago, IL] from: the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing (Gershenwald JE, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, ed. *AJCC Cancer Staging Manual*. 8th ed. New York: Springer International Publishing; 2017:563–585). CNS = central nervous system; 8e = AJCC Cancer Staging Manual 8th edition; LDH = lactate dehydrogenase.

In the 8e multivariable melanoma-specific survival (MSS) analysis of 7565 T1N0 patients (17), 0.8-mm tumor thickness threshold, mitotic rate (MR, dichotomized as <1 vs ≥1 mitosis/mm^2), and ulceration were evaluated. Based on these analyses, T1a is defined as nonulcerated and less than 0.8 mm, and T1b as 0.8–1.0 mm (regardless of ulceration status) or ulcerated if less than 0.8 mm (15,17).

Primary tumor ulceration is an adverse prognostic factor for node-negative patients and patients with stage III disease (16,23–30). In the 8e, ulceration is designated as absent or present in each T category; patients with ulcerated primary melanomas have outcomes similar to those without ulceration in the next highest T category (Figure 2A) (15–17,31).

Numerous studies have shown a negative association between MR and survival (19,32–39). Based on these studies, MR was incorporated as a dichotomous variable and T1 subcategory criterion in the 7e. Although MR was not a statistically significant factor (as a dichotomous variable) for T1 MSS in the 8e analyses and was removed as a T1 criterion, increasing MR as a continuous variable was associated with decreasing MSS among patients with clinically node-negative primary melanoma (Figure 2B) (17). MR continues to have important prognostic value regardless of thickness and is associated with increased risk of SLN metastasis (15,17,37–41). The AJCC MEP and National Comprehensive Cancer Network (NCCN) guidelines recommend that MR be recorded for all primary melanomas (17, 42).

Other features of primary melanoma not included in the 8e that should be recorded include Clark level (18,20,43–48), presence and density of tumor-infiltrating lymphocytes (49–56), and lymphovascular invasion (57–61).

Stages I and II

8e pathological stage I and II subgroups are mostly unchanged from the 7e; pathological stage IA now includes T1bN0M0 (formerly stage IB), reflecting better survival of patients with T1b melanoma and pathologically negative SLNs (Table 1) (17). Because patients with clinically node-negative T2–T4 melanoma had to undergo SLNB for inclusion in 8e analyses (in contrast to the 7e), MSS was higher across pathological stages I–II groups compared with the 7e (as in the 7e such T2-T4 patients were included even if SLNB was not performed). Patients with stages IA–IIA melanoma have a favorable prognosis, with 5-year MSS of 94–99% (Figure 2C). Given the AJCC MEP's intentional preservation of anatomic (TNM) stratification for staging purposes and revisions to the stage III groups, as in the 7e, there is prognostic overlap between stage II and stage III patients, with 8e stage IIB and IIC patients having similar or slightly lower 5-year MSS compared with 8e stage IIIA and IIIB patients (Figure 2, C and D) (17). Thus, from a clinical perspective, high-risk resectable melanoma should include stage IIB and IIC disease (Figure 1). Ongoing (eg, NCT03553836) or proposed adjuvant clinical trials for high-risk SLNB-negative patients highlight the interest in exploring adjuvant approaches to mitigate risk of relapse.

Clinicopathological Features of Regionally Metastatic Melanoma

In the 8e, the N category includes extent and number of tumor-involved regional lymph nodes (RLNs) (Figure 1) (15). "Clinically occult" nodal metastases describe patients without

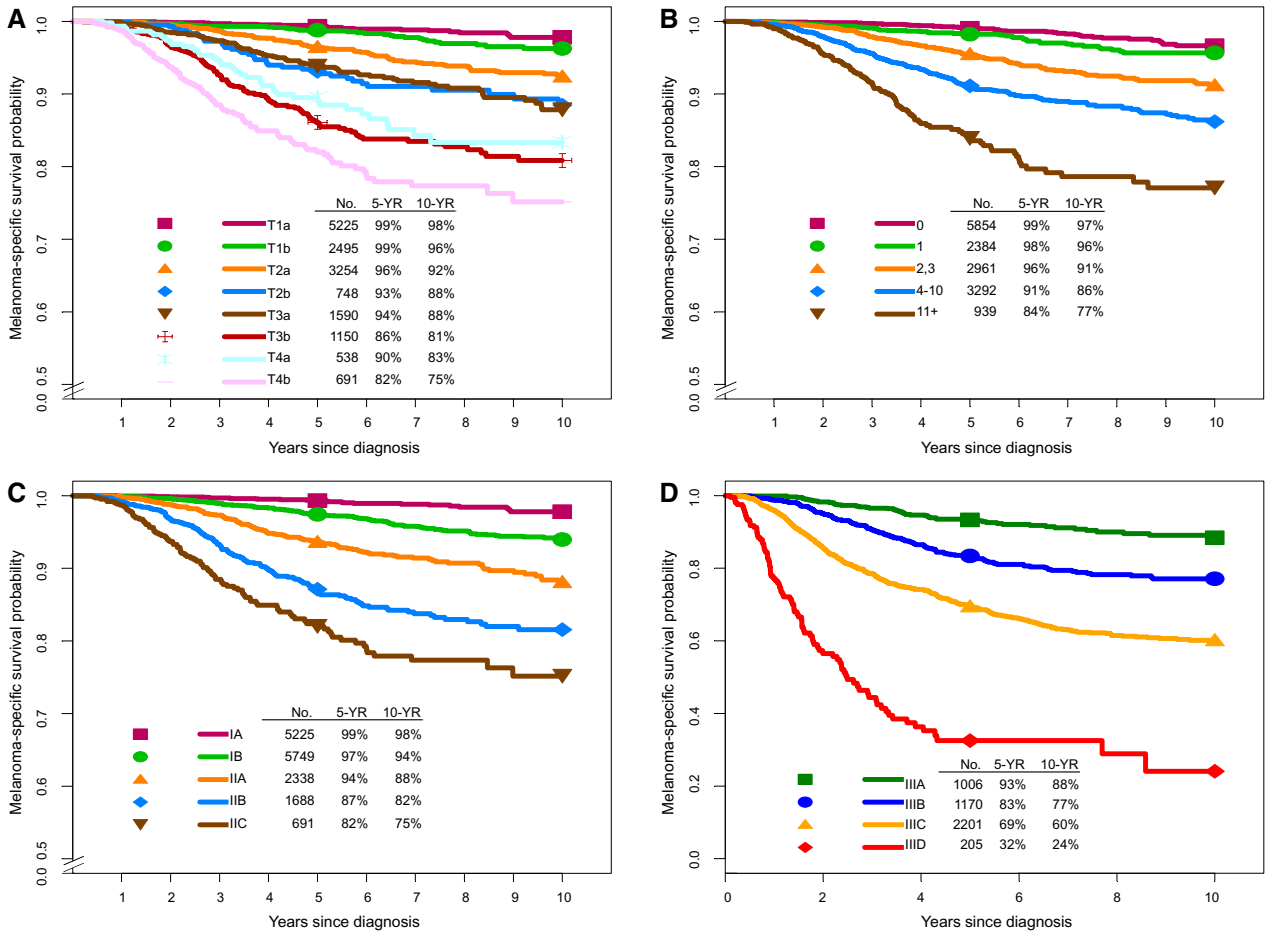

Figure 2. Melanoma-specific survival (MSS) according to T subcategory and mitotic rate (MR) for patients with stage I and II melanoma and according to stage I–III subgroups from the eighth edition International Melanoma Database.* MSS according to (**A**) T subcategory and (**B**) MR for patients with stage I and II melanoma, and according to (**C**) stage I–II subgroup and (**D**) stage III subgroup. *Adapted and used with permission from Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition Cancer Staging Manual. *CA Cancer J Clin*. 2017; 67:472–492. 2017 John Wiley & Sons, Inc.

clinical evidence of RLN metastasis who have RLN metastasis identified by SLNB (termed "microscopic" in the 7e). "Clinically detected" nodal metastases describe patients with RLN metastasis detected by clinical or radiographic examination (termed "macroscopic" in the 7e) (15). Patients with clinically occult vs clinically detected regional disease generally have longer survival (29,45,62,63), although prognosis varies (Figure 2D) (15,16,29). The number of tumor involved RLNs is an important predictor of survival (Figure 2D) (44,64,65). Patients with clinically occult or clinically detected RLN metastases are subcategorized based on the number of tumor-involved nodes (15) (Figure 1).

Extranodal tumor extension (ENE) or extracapsular extension, defined as a nodal metastasis extending through the lymph node (LN) capsule into adjacent tissues, usually occurs with large clinically detected nodal metastases that demonstrate gross effacement of normal nodal architecture but are occasionally observed with smaller LN metastases. Although not included as an 8e N category criterion, it is recommended that ENE be recorded (15,17,66).

Presence of microsatellite, satellite, or in-transit metastases, thought to represent intralymphatic or angiotrophic metastases (44,67–74), constitute 8e N category nonnodal locoregional components (Figure 1). As there was no substantial difference in survival in 8e univariate analysis among these entities, they were grouped for staging and are designated N1c, N2c, or N3c depending on the number of involved RLNs (Figure 3) (17).

Stage III

RLNs are the most common first metastatic site among patients with cutaneous melanoma. In the 8e, the N category includes patients with metastatic disease in RLNs and/or nonnodal locoregional sites (Figure 1). Patients with stage III melanoma have heterogeneous prognosis, with 5-year MSS varying from 32% to 93% depending on primary tumor characteristics, tumor burden within RLNs, number of RLNs involved, and presence of nonnodal locoregional metastases (17). Clinical management and design of future adjuvant therapy clinical trials should therefore reflect the wide variation in outcomes across stage III subgroups.

Although most patients with metastatic melanoma present with a known primary tumor, up to 10% of patients (with some higher estimates) with nodal metastases at diagnosis have no identifiable primary tumor and no history of primary melanoma (75–78). These patients demonstrate similar if not better

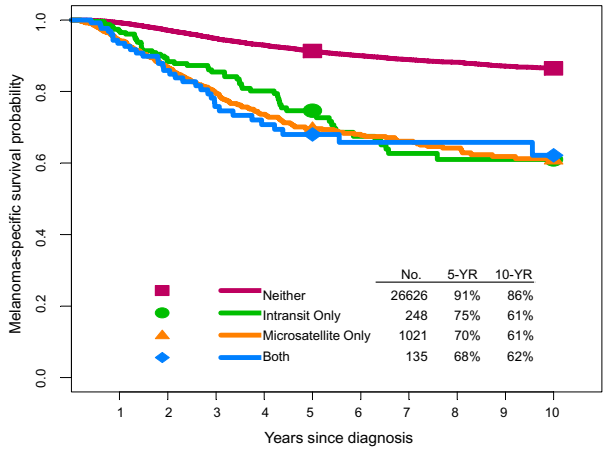

Figure 3. Melanoma-specific survival according to presence of in-transit or satellite disease from the eighth edition International Melanoma Database.* *Adapted and used with permission from Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition Cancer Staging Manual. *CA Cancer J Clin*. 2017; 67:472–492. 2017 John Wiley & Sons, Inc.

prognosis than those with regional metastatic melanoma from a known primary site (76,77). Because the natural history of stage III melanoma from an unknown primary site is comparable with that of stage III melanoma with a known primary melanoma (1,79–84), patients with regional metastatic melanoma (LN involvement and/or pathologically confirmed skin or subcutaneous melanoma metastases) and no known primary site should be classified as stage III if distant metastases are not identified by appropriate evaluation and considered for surgery along with neoadjuvant and adjuvant treatment (15).

Clinicopathological Features of Melanoma Distant Metastasis

The 8e analysis yielded several changes from the 7e with respect to categorization based on site of distant metastasis (Table 1) (15,17). Patients with distant metastasis to the skin, subcutaneous tissue, muscle, or LNs are again categorized as M1a and have a more favorable prognosis than patients with another distant metastasis (16,83,85–88). Patients with lung metastasis are again categorized as M1b. Patients with central nervous system (CNS) disease have the worst prognosis (89–92) and have been frequently excluded from clinical trials, particularly if metastases are untreated and/or active (3,4,6–8,93–103). A new 8e subcategory (M1d) was added to stratify patients with CNS disease, given the importance of CNS metastasis in clinical decision-making and to facilitate clinical trial design, stratification, and analysis, as therapeutic options for these patients are actively explored (93,94,97,102,104,105). Patients with non-CNS visceral metastasis now constitute a refined M1c category.

Patients with distant metastasis and elevated serum lactate dehydrogenase (LDH) have worse survival compared with patients with similar sites of metastasis and normal LDH (15,16,84,106–113). Even with effective systemic therapies, elevated LDH level is negatively associated with response, progression-free survival, MSS, and overall survival (OS) (107–109,114–116). To better account for these associations, each 8e M subcategory now includes an LDH-related suffix ("[0]", not elevated; "[1]", elevated) to provide additional granularity for clinical decision-making and for clinical trial design, stratification, and analysis (15).

Stage IV

Treatment options have improved for patients with stage IV melanoma during the past 8 years. Because long-term survival data are not yet available for the most contemporary and still-evolving treatment approaches, the AJCC 8e MEP concluded that it was premature to embark on a broad-based analytic initiative. Rather, the 7e stage IV international database, which included patients who presented with or developed stage IV disease through 2008, supplemented by published clinical trial data, was used (3–8,16,96–103,117,118).

Surgical Approach to High-Risk Resectable Melanoma

Resection Margins

Prospective randomized controlled trials (RCTs) have investigated the optimal surgical resection margins for primary cutaneous melanoma and are incorporated into NCCN guidelines (42); they are sometimes modified to accommodate functional and/or anatomic considerations. There is ongoing interest in exploring a narrower surgical resection margin for patients with Breslow thickness greater than 2 mm or 1–2 mm with ulceration (pT2b-pT4b, AJCC 8e) in an ongoing phase III, multicenter, non-inferiority-based RCT comparing 1-cm vs 2-cm margins (NCT03860883). Implications of narrower resection margins include decreased surgical morbidity and improved patient-reported outcomes; risks of decreased locoregional disease control and increased recurrence rate may be mitigated in this era of more effective systemic therapies.

The Role of SLNB and Lymphadenectomy

Although the most common site of melanoma metastasis is the RLN basin, most RLN metastases are clinically occult. Lymphatic mapping and SLNB to identify RLN metastases are the standard for RLN basin evaluation and staging for patients with cutaneous melanoma 1 mm or more in thickness (12,13,119–121). Because the risk of harboring occult RLN disease has been shown to be greater than or equal to 5% (and a minimum threshold for many clinicians to offer the procedure to otherwise healthy patients) for most patients with a primary tumor 0.8 mm or larger, for tumors 0.8–1.0 mm in thickness, NCCN guidelines state that SLNB may be discussed and considered, although there is no uniform consensus defining "high-risk features" in this prevalent patient group (40,42,122).

In 1999, Gershenwald et al. reported that SLN status was the most statistically significant prognostic factor for disease-free survival and MSS (121). These findings have been corroborated in subsequent literature (13,14,123–125), including the landmark Multicenter Selective Lymphadenectomy Trial-I (MSLT-I), which confirmed the prognostic significance of the SLN. Until recently, CLND was recommended for most patients with a positive SLNB (42). However, CLND carries risks, including wound infections and lymphedema. Furthermore, because only 10–20% of SLN-positive patients have tumor-involved non-SLNs at CLND, SLNB alone may be sufficient to confer the survival benefit seen in a subset of MSLT-I patients (14).

To address this question, two multicenter RCTs (DeCOG-SLT, MSLT-II) evaluated immediate CLND in patients with a positive SLN compared with nodal observation with or without ultrasound and showed that CLND did not provide clinically or statistically significant MSS benefits over nodal observation (14,126). Although prognostic information and regional control were improved with CLND, increased lymphedema was associated with CLND in both studies. Current NCCN guidelines recommend either nodal basin ultrasound surveillance or consideration of CLND for SLN-positive melanoma (42); however, the results of DeCOG-SLT and MSLT-II are clearly practice-changing and have begun to markedly reduce the fraction of SLN-positive patients undergoing CLND. Consideration of which patients, if any, benefit from CLND, as well as determining the "new" natural history of patients who do not undergo CLND in this era of more effective systemic therapy, are areas of ongoing clinical interest.

The evolving role of CLND coincides with an increase in more effective adjuvant therapy options. Importantly, it remains unclear the extent to which potential loss of prognostic information from CLND (ie, non-SLN tumor involvement as part of multivariable modeling and/or as a mechanism by which some patients may be upstaged to a higher stage III subgroup) affects decision-making regarding adjuvant therapy. Because the likelihood of patients with 8e stage IIIA melanoma having non-SLN tumor involvement on CLND is estimated to be quite low based on prior risk models, few would likely be upstaged (127,128). Prognostic models are currently being developed that may obviate the importance of non-SLN information for staging and decision-making purposes (129).

Adjuvant Therapy for High-Risk Resected Melanoma

The introduction of new targeted therapies and immune checkpoint inhibitors has markedly changed the adjuvant treatment landscape for patients with high-risk resected melanoma. Prior to this, adjuvant treatment was largely restricted to interferon therapy and limited by its poor tolerability and adverse events (AEs) that affect quality of life (130–132). Targeted combination regimens of BRAF and mitogen-activated protein kinase kinase (MEK) inhibitors, including dabrafenib plus trametinib, vemurafenib plus cobimetinib, and more recently, encorafenib plus cobimetinib, have improved outcomes for patients whose tumors test positive for the *BRAF* V600 driver mutation vs BRAF inhibitor monotherapy (4,5,11,99,101,109,117,133,134). Immune checkpoint inhibitors (anti-CTLA-4 and anti-PD1 antibodies) have also demonstrated favorable results, first for unresectable or metastatic melanoma and subsequently in the adjuvant setting (6,8,100,135,136).

Adjuvant Anti-CTLA-4 Therapy

Adjuvant ipilimumab, an anti-CTLA-4 therapy, was approved after demonstrating improved efficacy (recurrence-free survival [RFS]; distant metastasis-free survival; OS) compared with placebo in a phase III RCT in patients with high-risk resected melanoma (135,136) despite marked immune-related AEs and some deaths.

Adjuvant Anti-PD-1 Therapy

Following approval of adjuvant ipilimumab, nivolumab was compared with ipilimumab in the adjuvant setting for resected AJCC 7e stage IIIB, IIIC, or IV melanoma in the double-blind RCT CheckMate-238 (NCT02388906) (10). Patients in the nivolumab arm experienced statistically significantly longer RFS at 1 year (70.5% vs 60.8%, $P < .001$) and fewer grade 3 and 4 AEs (14.4% vs 45.9%). More patients completed 1 year of treatment (60.8% vs 26.9%) and fewer discontinued treatment (9.7% vs 42.6%) in the nivolumab vs ipilimumab arm. Based on these results, nivolumab received FDA approval for patients with LN involvement or metastatic disease who have undergone complete resection.

In KEYNOTE-054 (NCT02362594) (9), pembrolizumab was compared with placebo in patients with completely resected AJCC 7e stage III melanoma, with patients eligible for crossover to pembrolizumab upon disease recurrence. Eligible patients had either AJCC 7e stage IIIA melanoma (patients with stage IIIA melanoma had to have ≥1 LN metastasis >1 mm in greatest diameter) or IIIB or IIIC disease. Patients who received adjuvant pembrolizumab had a statistically significantly higher 1-year RFS (75.4% vs 61.0%, $P < .001$) with benefit independent of tumor PD-L1 status (9). In a recent post hoc analysis, AJCC 8e stage III subgroup had strong prognostic significance (with a caveat that longer follow-up is required to better assess treatment impact in the AJCC 8e stage IIIA cohort), as demonstrated by 1-year RFS rates with pembrolizumab vs placebo (IIIA, 92.7% vs 92.5%; IIIB, 79.0% vs 65.5%; IIIC, 73.6% vs 53.9%; IIID, 50.0% vs 33.3%), suggesting that treatment recommendations may need to be tailored to stage III subgroup (137).

Although most clinicians currently favor anti-PD-1–based approaches based on risk-benefit results to date, longer follow-up of RCTs evaluating adjuvant anti-PD-1 therapy will be needed to determine whether they improve MSS (138).

Adjuvant Targeted Therapies

For the approximately 40–50% of patients with *BRAF* V600-mutant melanoma, combined BRAF plus MEK inhibition with dabrafenib plus trametinib has resulted in improved survival in patients with this driver-mutation (3–5,109,115,139–141). In the COMBI-AD trial, patients with AJCC 7e stage IIIA (patients with stage IIIA melanoma had to have ≥1 LN metastasis >1 mm in greatest diameter), IIB, or IIIC *BRAF* V600-mutant melanoma who received adjuvant dabrafenib plus trametinib experienced statistically significantly higher 3-year RFS (58% vs 39%, $P < .001$) and 3-year OS (86% vs 77%, $P = .0006$) compared with placebo (11), with similar AEs to those reported in patients with *BRAF* V600-mutant metastatic melanoma (3–5,98,109,115). Most patients completed 1 year of scheduled treatment; however, 26% discontinued therapy due to AEs. Dabrafenib plus trametinib was approved by the FDA in April 2018 for the adjuvant treatment of *BRAF* V600E/K-mutant melanoma, and unlike CheckMate-238 and KEYNOTE-054, COMBI-AD included an early OS readout. Interestingly, in a recent exploratory analysis of extended study follow-up, RFS benefit was also observed across all AJCC 8e stage III subgroups (142), supporting that AJCC 8e and planned integrative risk models may help to inform ICB-related clinical decision-making going forward.

Adjuvant Radiation Therapy

In select circumstances, adjuvant radiation therapy (RT) can be considered for patients with high-risk resected melanoma. Multiple retrospective studies reported improved regional disease control in patients at high risk of relapse who undergo lymphadenectomy and receive adjuvant RT to nodal basins (143–146). Features associated with increased risk of regional failure include multiple positive LNs, 1 or more large node(s), ENE, and extranodal disease (147–151). A prospective, multicenter, phase III RCT (ANZMTG 01.02/TROG 02.01) in patients at high risk for LN field relapse after therapeutic lymphadenectomy demonstrated that adjuvant regional RT decreased the risk of local recurrence compared with nodal basin observation only, often with increased risk of lymphedema without improvement in OS (152,153). In view of these data, combined with exciting developments in the adjuvant systemic therapy arena, the role of adjuvant RT for high-risk resected melanoma remains limited but should be discussed with patients at high risk of nodal failure after lymphadenectomy in the context of a multidisciplinary team approach.

Advances on the Horizon: Neoadjuvant Therapy for High-Risk Resectable Melanoma

Rationale

Interest in evaluating targeted therapies and immune checkpoint inhibitors in the neoadjuvant setting for locally and regionally advanced melanoma is growing (Supplementary Table 1 available online) (154). Neoadjuvant treatment may also facilitate surgical resection in patients with locally advanced disease who are at high risk for incomplete resection or positive resection margins, or in whom upfront surgery may not be feasible. Neoadjuvant approaches using chemotherapy and chemoradiation have been shown to improve survival and/or surgical outcomes in patients with multiple other solid malignancies (155–168). Neoadjuvant biochemotherapy in melanoma patients with locoregional metastases has also been explored (169).

Efficacy of systemic therapy can be evaluated preoperatively by monitoring tumor response and postoperatively by pathological evaluation of the resected tumor (170). Preclinical and early clinical studies suggest that neoadjuvant checkpoint blockade may facilitate resectability of high-risk or borderline resectable lesions and may improve recurrence and survival compared with adjuvant therapy (171–173).

Clinical Trials of Neoadjuvant Targeted Therapies and Immune Checkpoint Blockade in Resectable Stages III and IV Melanoma

Neoadjuvant trials include ongoing or actively recruiting early-phase studies of targeted combination therapy and ICB (Supplementary Table 1 available online). Interim analysis of the Combi-Neo trial (NCT02231775), in which patients with stage IIIB or IIIC or oligometastatic stage IV *BRAF*-mutant melanoma were randomly assigned to up-front surgery vs neoadjuvant combination dabrafenib plus trametinib, demonstrated a high pathological complete response rate (58%) along with statistically significantly improved event-free survival (median 19.7 vs 2.9 months, $P < .0001$) over surgery (174), and in the single-arm NeoCombi trial (NCT01972347) of 40 patients receiving neoadjuvant dabrafenib plus trametinib, 86% achieved RECIST response with a 49% pathological complete response rate (175).

Two studies of neoadjuvant ICB recently reported results. Blank et al. reported a randomized, phase Ib study to test the feasibility and compare the efficacy of neoadjuvant ipilimumab plus nivolumab with adjuvant therapy using the same regimen (NCT02437279) (176,177), and Amaria et al. reported a randomized, phase II study of neoadjuvant nivolumab vs ipilimumab plus nivolumab in 23 patients (NCT02519322) (178). Both studies found that neoadjuvant ipilimumab plus nivolumab combination therapy was associated with high response rates, albeit with clinically significant toxicity. Recent pooled analysis data from the International Neoadjuvant Melanoma Consortium also suggest that there may be durable prognostic significance associated with extent of pathological response to neoadjuvant therapy (179). A single-institution pilot study suggests that extent of surgery (eg, surgical removal of the "index" node) following neoadjuvant therapy represents an exciting new area of investigation (180).

The open-label, phase II OpACIN-neo (NCT02977052) trial randomly assigned patients to receive varying doses and sequences of ipilimumab and nivolumab followed by surgical resection (181) and identified a tolerable neoadjuvant dosing schedule (ipilimumab 1 mg/kg plus nivolumab 3 mg/kg) that might be suitable for broader clinical use. Other phase I and II studies will also provide insight into combining ICB with targeted therapies, oncolytic viral therapy, biochemotherapy with interferon, or other novel therapies (Supplementary Table 1 available online).

With increased interest in and use of neoadjuvant targeted and immune therapies, it is critical that clinical trial designs and correlative analyses across studies are aligned to facilitate comparison of results and optimal data organization for future regulatory review and to further strengthen translational research. Since 2016, the International Neoadjuvant Melanoma Consortium has met regularly to identify and address opportunities and challenges in establishing neoadjuvant systemic therapy among treatment options for high-risk, resectable melanoma and has recently published two white papers setting forth recommendations and guiding principles for neoadjuvant research, including pathological assessment of resection specimens (170,182).

Future Directions

Advances in our understanding of melanoma pathogenesis have led to the introduction of molecularly targeted therapies and immune checkpoint inhibitors that have improved the outlook and prognosis for melanoma patients. Simultaneously, the role and sequencing of surgery in the multimodal treatment of high-risk resectable and advanced and oligometastatic melanoma is evolving following the results of MSLT-II and DeCOG-SLT and development of effective systemic therapies. Neoadjuvant approaches have the potential to transform the treatment landscape in high-risk resectable stage III melanoma. Taken together, these advances offer exciting opportunities to further refine the development and validation of prognostic models, clinical tools, and future staging and risk stratification systems that incorporate data reflective of the contemporary era in which patients are routinely offered targeted- and immune-based therapies.

Currently, there is much enthusiasm surrounding the development of integrated risk models and clinical tools that

enhance predictive and prognostic assessment and clinical decision-making. The ability to identify patients with higher risk than that predicted by conventional staging would assist clinicians in refining the use of adjuvant therapy or more comprehensive follow-up. Ongoing efforts to identify predictors of response and mechanisms of resistance to targeted therapies and immunotherapies, the evolving role of the microbiome, and other molecular and immunological signatures will help inform individualized prognostic and predictive models that can guide multidisciplinary care (17,129,183,184).

Despite these advances, many unmet needs remain. As fewer patients with tumor-involved SLNs undergo CLND, questions arise regarding the prognosis of and optimal systemic therapy for patients with stage III disease. The 8e staging system may have identified a favorable subset of patients with regional nodal disease (eg, stage IIIA and possibly IIIB) for whom adjuvant therapy may not be routinely recommended; development and validation of individualized integrated risk models are underway to further inform contemporary clinical decision-making. Whether results of CheckMate-238 and/or COMBI-AD are applicable for all patients with clinically occult nodal disease remains an area of ongoing interest. Going forward, we will continue to observe and better understand the natural history and prognosis of an increasingly prevalent group of patients with clinically occult RLN metastasis who do not undergo CLND. The role and impact of CLND at the time of regional failure in these patients remains an unanswered question. Lastly, further research is required in many melanoma patient subgroups, including those who cannot receive ICB, who relapse following first-line adjuvant therapy, have *BRAF* wild-type melanoma, have brain metastases, and/or have less prevalent melanoma subtypes such as uveal and mucosal melanoma, for whom effective treatment options remain limited and/or outcomes in advanced-stage disease remain poor.

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