Cutaneous Melanoma, Version 2.2019

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ABSTRACT

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Cutaneous melanoma have been significantly revised over the past few years in response to emerging data on immune checkpoint inhibitor therapies and BRAF-targeted therapy. This article summarizes the data and rationale supporting extensive changes to the recommendations for systemic therapy as adjuvant treatment of resected disease and as treatment of unresectable or distant metastatic disease.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

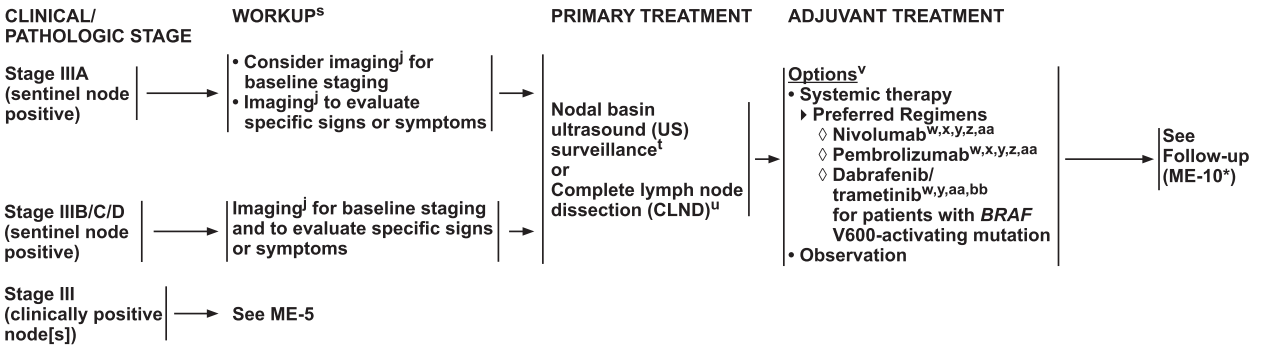
The complete NCCN Guidelines for Cutaneous Melanoma are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

Disclosures for the NCCN Cutaneous Melanoma Panel

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

Individual disclosures for the NCCN Cutaneous Melanoma Panel members can be found on page 402. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



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

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

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

[u]For patients with a positive sentinel node, two prospective randomized phase III studies have demonstrated no improvement in melanoma-specific survival or OS in patients undergoing CLND compared to those who underwent nodal basin US surveillance. CLND did provide additional prognostic information as well as improvement in regional control/recurrence at the expense of increased morbidity, including wound complications and long-term lymphedema. Factors that predict non-SLN positivity include sentinel node tumor burden, number of positive nodes, and thickness/ulceration of the primary tumor.
See Principles of Complete Lymph Node Dissection (ME-G*).

[v]The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.

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

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

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

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

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

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

*Available online, in these guidelines, at NCCN.org.

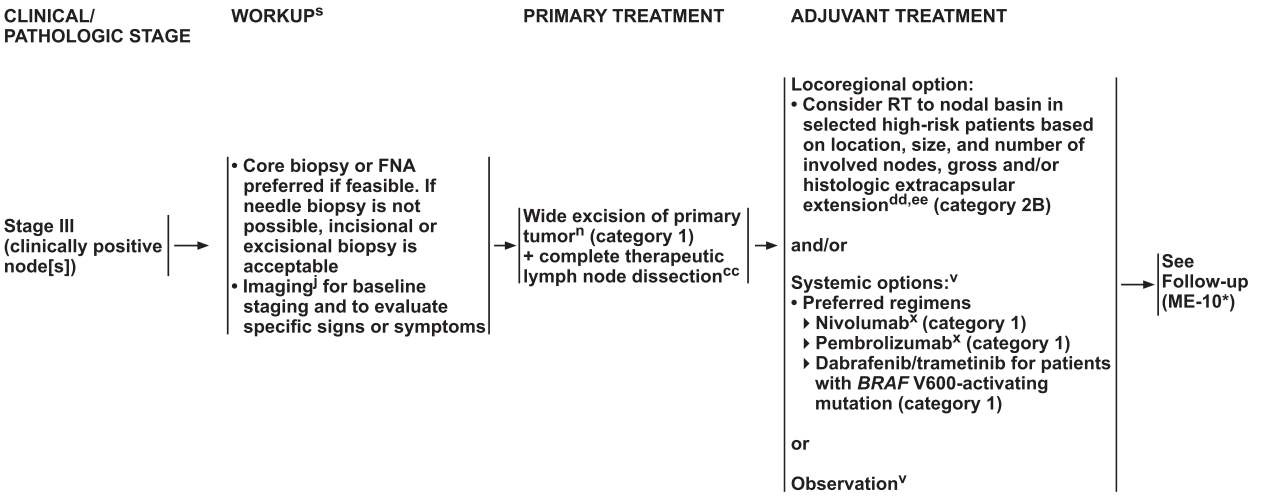
Adjuvant Systemic Therapy for Melanoma

Brief History of Adjuvant Therapy Options for Melanoma

For adjuvant treatment of melanoma in patients rendered free of disease by surgery, traditional systemic therapy approaches have proven to be ineffective. Adjuvant interferon alfa (IFN alfa), particularly high-dose IFN alfa, has been widely used in patients with melanoma for many years. A large body of clinical evidence has amassed from prospective randomized trials comparing adjuvant IFN alfa with observation or control treatments now thought to be ineffective in melanoma. Results varied across trials, with some showing improvement in relapse-free survival (RFS),[1–9] a few showing improvement in overall survival (OS),[3,5,6,8] but others showing no improvement in RFS or OS, or effects with borderline statistical significance.[6,7,10–17] Meta-analyses including data from a large number of trials have shown that improvements in RFS and OS are statistically significant but small. A recent meta-analysis reported improvements in 5- and 10-year event-free survival and OS of less than 4%.[18]

IFN alfa has been supplanted, however, by targeted therapy and immune checkpoint inhibitor options based on results from recent and ongoing prospective randomized trials.[19–23] Although trials supporting immune checkpoint inhibitor and targeted therapy as adjuvant treatment options did not compare these agents to IFN alfa, the NCCN melanoma panel considers these agents to be more effective and better tolerated than IFN alfa, and therefore no longer recommends IFN alfa for adjuvant treatment of cutaneous melanoma.

For several years, biochemotherapy was among the listed options for adjuvant treatment of resected high-risk stage III melanoma. Inclusion of biochemotherapy as an adjuvant option was based on results from the SWOG S0008 phase 3 randomized trial showing that the combination of cisplatin, vinblastine, dacarbazine, IL-2, and IFN alfa improved RFS compared with high-dose IFN alfa-2b (median of 4.0 vs 1.9 years; HR, 0.75 with 95% CI, 0.58–0.97; $P=.03$).[24] Although the studies supporting adjuvant immune checkpoint inhibitor and targeted therapy options did not compare these newer approaches with biochemotherapy, the latter has been removed from the list of adjuvant options because it was rarely being used at NCCN Member Institutions due both to its high toxicity profile and to the emergence of more effective adjuvant therapy options.



[j]See Principles of Imaging–Workup (ME-D*).
[n]See Principles of Surgical Margins for Wide Excision of Primary Melanoma (ME-E*).
[s]*BRAF* mutation testing is recommended for patients with stage III at high risk for recurrence for whom future BRAF-directed therapy may be an option. See Principles of Molecular Testing (ME-C*).
[v]The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.
[x]Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported.
[cc]In patients with borderline resectable lymphadenopathy or very high risk of recurrence after lymphadenectomy, consider a clinical trial of neoadjuvant systemic therapy.
[dd]Adjuvant nodal basin RT is associated with reduced lymph node field recurrence but has shown no improvement in RFS or OS. Its benefits must be weighed against potential toxicities such as lymphedema (limb) or oropharyngeal complications. The impact of these potential toxicities should be considered in the context of other adjuvant treatment options.
[ee]See Principles of Radiation Therapy for Melanoma (ME-H*).

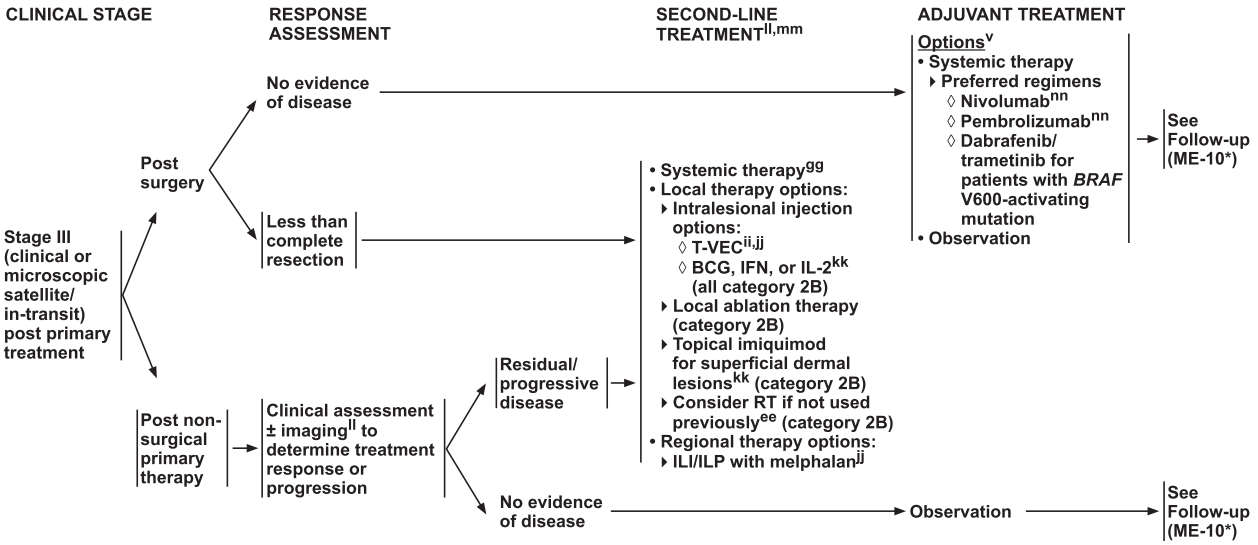
*Available online, in these guidelines, at NCCN.org.

NCCN Recommendations for Considering Adjuvant Systemic Therapy

Adjuvant treatment outside of a clinical trial is not recommended for patients with stage I/II disease, although the rationale for this recommendation varies across the NCCN panel. There are no FDA-approved adjuvant immune checkpoint inhibitors or BRAF-targeted therapies for this group of patients. Although most of the trials to date did not include patients with stage I/II disease (Table 1), clinical trials are underway to define the role of adjuvant checkpoint inhibitors in high-risk stage II patients (ClinicalTrials.gov identifiers: NCT3553836 and NCT03405155).

For patients with resected advanced melanoma, there have been a number of prospective randomized trials suggesting that immune checkpoint inhibitor and BRAF-targeted therapy are effective options for adjuvant treatment. Data from these trials are summarized in Table 1. These trials, the FDA-approved indications (Table 2), and the NCCN recommendations (Table 3) based on these trials are discussed in greater detail in subsequent sections. Selection of a specific adjuvant systemic therapy for patients with resected advanced melanoma depends on many factors, including risk of recurrence, potential clinical benefit, potential toxicities, patient preference, patient age, and comorbidities. Other options include participation in a clinical trial and observation.

The most important factor to consider is the risk of recurrence and/or death from disease. Stage IIIA is the lowest risk group for which the NCCN Guidelines recommend considering adjuvant treatment. Several of the recent phase III randomized trials testing immune checkpoint inhibitors or BRAF-targeted therapies have included some stage IIIA patients; generally, the trials have included only those sentinel node–positive patients with a nodal metastasis at least 1 mm in diameter, as these were judged to be higher risk (Table 1). It is important to note, however, that the entry criteria for these trials were based on AJCC 7th edition staging, and that patients with stage IIIA disease as defined by AJCC 7th edition staging comprise a higher risk group than stage IIIA as defined by AJCC 8th edition staging. The 8th edition staging also incorporates Breslow thickness into stage III disease (5-year melanoma-specific survival for AJCC 7th edition stage IIIA is 78%, compared with 93% for AJCC 8th edition stage IIIA).[25] In patients with resected stage III disease at low risk of recurrence (eg, AJCC 8th edition stage IIIA and/or those with sentinel



[v]The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.
[ee]See Principles of Radiation Therapy for Melanoma (ME-H*).
[gg]See Systemic Therapy for Metastatic or Unresectable Disease (ME-I 1 of 5).
[ii]T-VEC was associated with a response rate (lasting ≥6 months) of 16% in highly selected patients with unresectable metastatic melanoma. Efficacy was noted in AJCC 7th Edition stage IIIB and IIIC disease, and was more likely to be seen in patients who were treatment naive.
[jj]These options have been preference stratified as "Preferred Regimens."
[kk]These options have been preference stratified as "Useful In Certain Circumstances."
[ll]See Principles of Imaging–Treatment Response Assessment (ME-D*).
[mm]For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and not of same class. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered.
[nn]Nivolumab has shown a clinically significant improvement in RFS compared to high-dose ipilimumab, but its impact on OS has not yet been reported. Pembrolizumab has shown a clinically significant improvement in RFS compared to placebo, but its impact on OS has not yet been reported. Although both trials focused primarily on patients with stage III nodal disease, the NCCN panel agrees that it is appropriate to extend the indication for adjuvant anti-PD-1 therapy to patients with clinical or macroscopic satellite/intransit disease and who are at significant risk of recurrence.

*Available online, in these guidelines, at NCCN.org.

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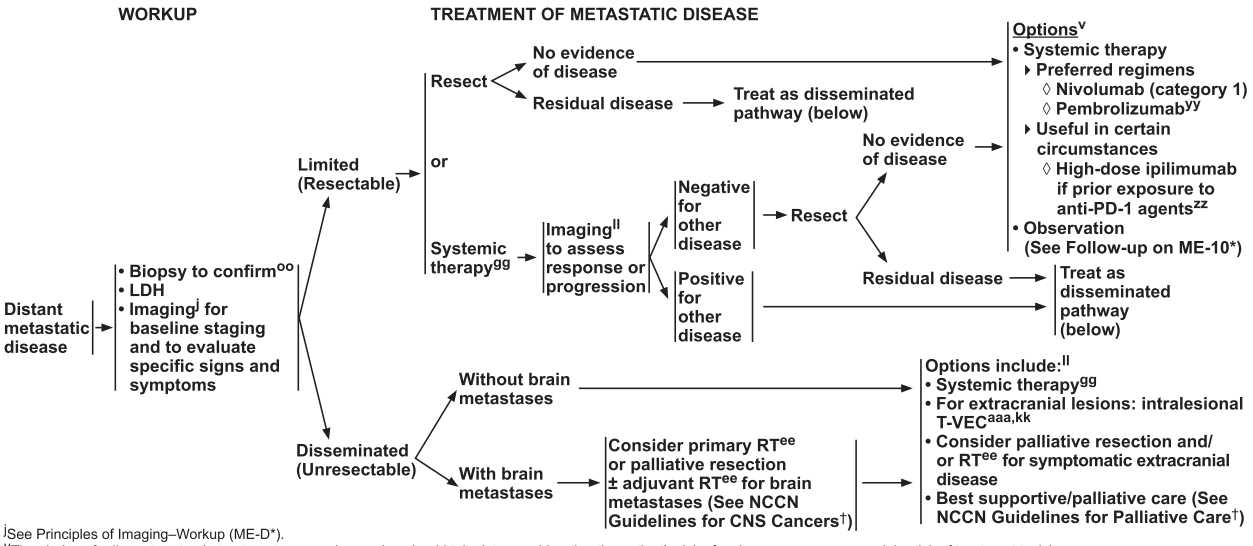
lymph node [SLN] metastasis <1 mm), the toxicity of adjuvant therapy may outweigh the benefit, and should be discussed with the patient.

Across the NCCN panel, opinions vary regarding the strength of evidence supporting adjuvant systemic therapy (using the currently recommended options shown in Table 3) for resected stage III/IV disease. NCCN panel members agree that recommendations for systemic adjuvant treatment (Table 3) are supported by improvements in RFS as reported in recent and ongoing prospective randomized trials (Table 1). Some panel members believe that RFS improvement and available survival data suggest that up-front adjuvant systemic therapy is preferable, and expect that further follow-up will confirm that adjuvant treatment (with the currently recommended agents) improves disease-specific survival. Other panel members are less convinced by the available data and would prefer to wait for longer term follow-up confirming that the observed improvement in RFS translates into improvement in OS/disease-specific survival (DSS) before making a strong case for using up-front adjuvant treatment in most patients with stage III disease. The argument against routine adjuvant therapy for all patients with resected stage III disease is that, unless the observed improvement in RFS translates into a corresponding improvement in OS/DSS, a more selective approach to the use of adjuvant therapy may be prudent, with the idea that forgoing up-front adjuvant therapy and then treating in the event of relapse may result in similar OS/DSS but lower overall risk of toxicity.

When considering whether adjuvant therapy is appropriate for a patient with regional disease limited to clinically occult nodal metastases, it is also important to note that entry criteria for all the trials in Table 1 required complete resection of all disease, including primary tumor excision with adequate margins and complete lymph node dissection (CLND) in patients with nodal metastases detected by SLN biopsy (SLNB). However, based on results from 2 prospective randomized trials (MSLT-II and DeCOG) demonstrating that CLND did not improve DSS or OS in patients with clinically occult nodal disease,[26,27] it is reasonable to consider nodal basin ultrasound surveillance in lieu of CLND. Although it is unclear whether the recommended adjuvant treatment options have similar efficacy in the absence of CLND following a positive SLNB, the NCCN Melanoma Panel thinks that CLND should



[j]See Principles of Imaging–Workup (ME-D*).
[v]The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity.
[ee]See Principles of Radiation Therapy for Melanoma (ME-H*).
[gg]See Systemic Therapy for Metastatic or Unresectable Disease (ME-I).
[kk]These options have been preference stratified as "Useful In Certain Circumstances."
[ll]See Principles of Imaging–Treatment Response Assessment (ME-D*).
[oo]Initial presentation with stage IV disease or clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated. Biopsy techniques may include FNA, core, incisional, or excisional. Tissue is always preferred over cytology for mutational analysis. Obtain tissue to ascertain alterations in *BRAF*, and in the appropriate clinical setting, *KIT* from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Consider broader genomic profiling if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. See Principles of Biopsy and Pathology (ME-B*) and See Principles of Molecular Testing (ME-C*)
[yy]Although patients with resected stage IV disease were not included in the phase III prospective randomized trial testing adjuvant pembrolizumab, it is included as an option here because all available evidence suggests that pembrolizumab and nivolumab have highly similar efficacy and safety in patients with melanoma.
[zz]Ipilimumab is included as an adjuvant treatment option for patients with resected stage IV disease who have prior exposure to anti-PD-1 agents based on extrapolation of data demonstrating its efficacy as adjuvant treatment for resected stage III disease and demonstrated efficacy for unresectable stage IV disease.
[aaa]T-VEC has shown a response rate (lasting ≥6 months) of 16% in highly selected patients with AJCC 7th Edition stage IV-M1a disease (skin, subcutaneous, and/or remote nodes).
*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

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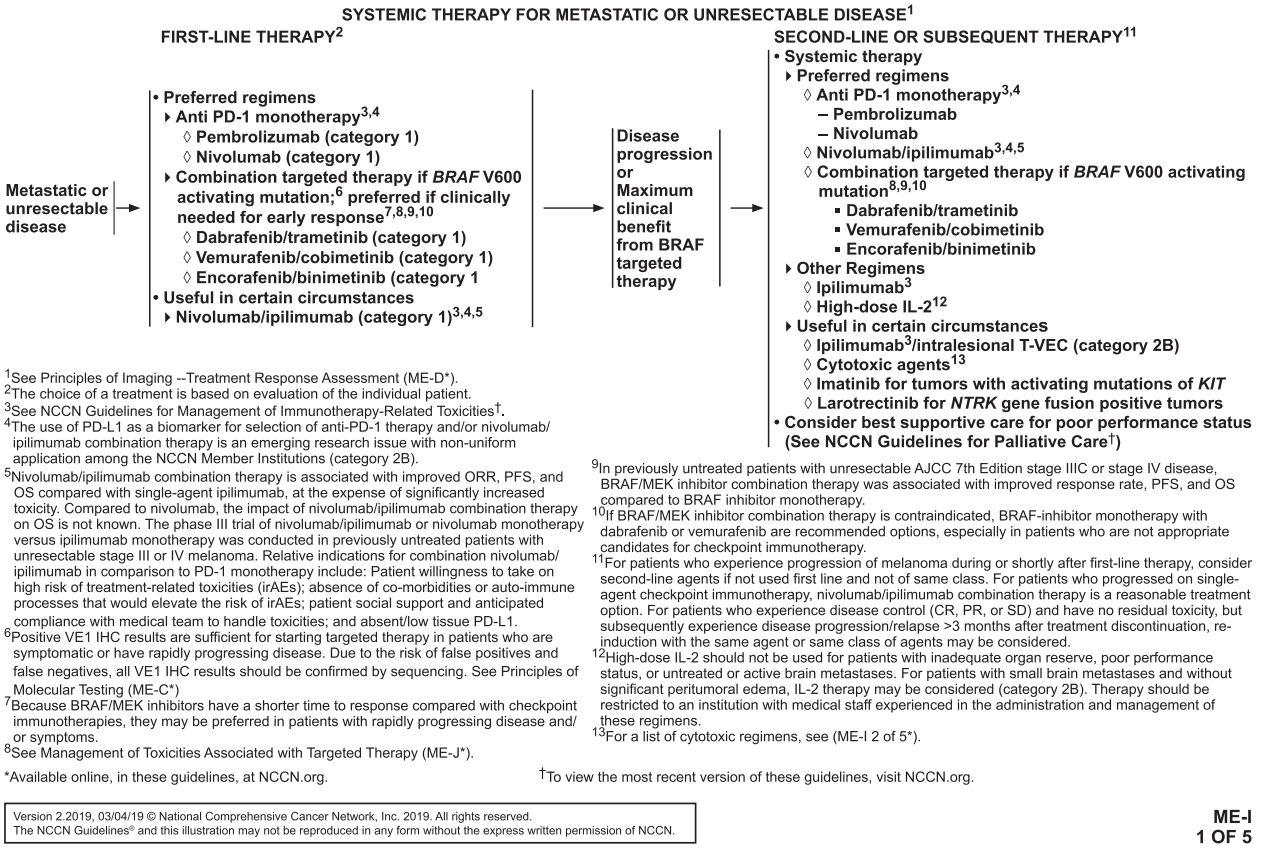
not be a factor in the decision to use adjuvant therapy in patients whose nodal metastases are detected by SLNB.

Risk of toxicity is the other major consideration when deciding whether a patient with stage III disease should receive adjuvant therapy. Table 1 includes adverse event (AE) rates observed in each of the prospective randomized trials testing immune checkpoint inhibitors and BRAF-targeted therapies in the adjuvant setting. Although anti-programmed cell death protein 1 (PD-1) agents and BRAF/MEK inhibitor therapy are associated with lower rates of toxicity than historical adjuvant therapy options (IFN alfa, biochemotherapy), grade 3-4 AEs (all cause) were observed in 25%–41% of patients treated in adjuvant trials,[21–23] and a small proportion of patients receiving adjuvant immune checkpoint inhibitors can develop life-long immune-related AEs (irAEs). In patients with prior exposure to anti-PD-1 therapy and for whom adjuvant ipilimumab is an option, the decision should be informed by careful consideration of a patient's individual risk of recurrence and their ability to tolerate and manage toxicities. Patients selected for the adjuvant trials shown in Table 1 all had good performance status (ECOG 0 or 1), and the immunotherapy trials also excluded patients with autoimmune disease or uncontrolled infection, and those requiring systemic glucocorticoids.[20–23] Before starting any adjuvant therapy, the NCCN panel recommends reviewing the U.S. prescribing information for each agent being considered, to ensure that contraindications are identified, and for dosing options and administration and recommendations. For monitoring and management of irAEs associated with immune checkpoint inhibitors, refer to the NCCN Guidelines for Management of Immunotherapy Related Toxicities (available at NCCN.org).

Specific Systemic Therapy Options for Adjuvant Treatment

A number of prospective randomized trials have shown that immune checkpoint inhibitors and BRAF-targeted therapies are effective for unresectable stage III and stage IV melanoma,[28–43] and these drugs are now FDA approved and widely used in this setting. The FDA approved indications are summarized in Table 2. Based on their efficacy for unresectable advanced disease, many of these therapies are now the subject of ongoing prospective randomized trials to determine whether they provide clinical benefit as adjuvant treatment of resected advanced disease.



[1]See Principles of Imaging --Treatment Response Assessment (ME-D*).
[2]The choice of a treatment is based on evaluation of the individual patient.
[3]See NCCN Guidelines for Management of Immunotherapy-Related Toxicities†.
[4]The use of PD-L1 as a biomarker for selection of anti-PD-1 therapy and/or nivolumab/ipilimumab combination therapy is an emerging research issue with non-uniform application among the NCCN Member Institutions (category 2B).
[5]Nivolumab/ipilimumab combination therapy is associated with improved ORR, PFS, and OS compared with single-agent ipilimumab, at the expense of significantly increased toxicity. Compared to nivolumab, the impact of nivolumab/ipilimumab combination therapy on OS is not known. The phase III trial of nivolumab/ipilimumab or nivolumab monotherapy versus ipilimumab monotherapy was conducted in previously untreated patients with unresectable stage III or IV melanoma. Relative indications for combination nivolumab/ipilimumab in comparison to PD-1 monotherapy include: Patient willingness to take on high risk of treatment-related toxicities (irAEs); absence of co-morbidities or auto-immune processes that would elevate the risk of irAEs; patient social support and anticipated compliance with medical team to handle toxicities; and absent/low tissue PD-L1.
[6]Positive VE1 IHC results are sufficient for starting targeted therapy in patients who are symptomatic or have rapidly progressing disease. Due to the risk of false positives and false negatives, all VE1 IHC results should be confirmed by sequencing. See Principles of Molecular Testing (ME-C*)
[7]Because BRAF/MEK inhibitors have a shorter time to response compared with checkpoint immunotherapies, they may be preferred in patients with rapidly progressing disease and/or symptoms.
[8]See Management of Toxicities Associated with Targeted Therapy (ME-J*).
[9]In previously untreated patients with unresectable AJCC 7th Edition stage IIIC or stage IV disease, BRAF/MEK inhibitor combination therapy was associated with improved response rate, PFS, and OS compared to BRAF inhibitor monotherapy.
[10]If BRAF/MEK inhibitor combination therapy is contraindicated, BRAF-inhibitor monotherapy with dabrafenib or vemurafenib are recommended options, especially in patients who are not appropriate candidates for checkpoint immunotherapy.
[11]For patients who experience progression of melanoma during or shortly after first-line therapy, consider second-line agents if not used first line and not of same class. For patients who progressed on single-agent checkpoint immunotherapy, nivolumab/ipilimumab combination therapy is a reasonable treatment option. For patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but subsequently experience disease progression/relapse >3 months after treatment discontinuation, re-induction with the same agent or same class of agents may be considered.
[12]High-dose IL-2 should not be used for patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. For patients with small brain metastases and without significant peritumoral edema, IL-2 therapy may be considered (category 2B). Therapy should be restricted to an institution with medical staff experienced in the administration and management of these regimens.
[13]For a list of cytotoxic regimens, see (ME-I 2 of 5*).

*Available online, in these guidelines, at NCCN.org.
†To view the most recent version of these guidelines, visit NCCN.org.

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Table 1 summarizes published efficacy and safety data from prospective randomized controlled trials testing some of these immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab) and targeted therapies (vemurafenib, dabrafenib/trametinib) for adjuvant treatment of high-risk resected melanoma. Based on data shown in Table 1, some of these therapies have now been approved for adjuvant treatment of resected melanoma (Table 2).

Most of the trials shown in Table 1 excluded patients who had received any kind of prior systemic therapy (EORTC 1807, COMBI-AD, CheckMate 238, KEYNOTE-054, BRIM8).[20–23,44] Each of these trials included a subset stage III disease deemed sufficiently high risk to warrant adjuvant treatment, but the definitions of "high risk" stage III differed across trials. Note that for all these trials AJCC 7th edition staging was used, whereas the NCCN Guidelines have been updated to reflect AJCC 8th edition staging (Table 3). The efficacy and safety data for each of these adjuvant therapies is described in greater detail subsequently.

Immune Checkpoint Inhibitors

Ipilimumab

Ipilimumab, a monoclonal antibody that binds and blocks the function of the immune checkpoint receptor cytotoxic T lymphocyte antigen-4 (CTLA-4), has been shown to significantly improve PFS and OS in patients with unresectable or metastatic melanoma,[28,29] and originally received FDA approval in 2011 for treatment of patients with metastatic melanoma. Based on its efficacy for treating metastatic disease, the phase 3 double-blind, randomized, multicenter, international EORTC 18071 trial compared adjuvant high-dose ipilimumab (10 mg/kg) with placebo in selected patients with completely resected stage III melanoma (Table 1).[19,20] Eligible patients included those with AJCC 7th edition stage IIIA disease (if N1a, at least 1 metastasis >1 mm), or with stage IIIB–C disease but no in-transit metastases. All patients had their primary tumor excised with adequate margins and complete regional lymphadenectomy, but none had received systemic therapy for melanoma.[19] The trial demonstrated that ipilimumab improved RFS, distant metastasis-free survival (DMFS) and OS (Table 1). Based on these results, the FDA approved high-dose ipilimumab as adjuvant treatment in melanoma. The FDA-approved indication includes all patient groups included in the trial, patients with stage III in-transit disease (provided they also have at least 1 nodal metastasis >1 mm diameter), and those who had received prior systemic therapy for melanoma.[19,45]

Table 1. Immune Checkpoint Inhibitor and Targeted Therapy: Randomized Trial Data for Adjuvant Treatment

Trial					Efficacy Analysis[b]			AEs[c]
Name and Reference	Phase Design	Stages Included[a]	Treatment Arms	Median Follow-up	RFS or DFS	DMFS	OS	Any Grade Grade 3–4 Grade 5
Immune Checkpoint Inhibitors								
EORTC 18071 NCT00636168 Eggermont et al,[20] 2016	III DB RCT	IIIA >1 mm, IIIB/C no IT	HD-Ipi (n=475) Pbo (n=476)	5.3 y	5-y: 41% vs 30% HR=0.76 [0.64-0.89] *P*<.001	5-y: 48% vs 39% HR=0.76 [0.64-0.92] *P*=.002	5-y: 65% vs 54% HR=0.72 [0.58–0.88] *P*=.001	99% vs 91% 54% vs 26% 1.5 vs 1.3%
CheckMate 238 NCT02388906 Weber et al,[21] 2017	III DB RCT	IIIB/C,[d] IV	Nivo + Pbo (n=453) HD-Ipi + Pbo (n=453)	1.6 y	1-y: 71% vs 61%[e] HR=0.65 [0.51–0.83] *P*<.001	1-y: 80 vs 73% HR=0.73 [0.55–0.95]	NR	97% vs 99% 25% vs 55% 0 vs 0.4%
KEYNOTE-054 NCT02362594 Eggermont et al,[22] 2018	III DB RCT	IIIA >1 mm, IIIB/C no IT[f]	Pembro (n=514) Pbo (n=505)	1.2 y	1-y: 75% vs 61% HR=0.57 [0.43–0.74] *P*<.001	NR[g]	NR	93% vs 90% 32% vs 19% 0.2% vs 0
BRAF-Targeted Therapy								
COMBI-AD NCT01682083 Long et al,[23] 2017	III DB RCT	IIIA >1 mm, IIIB/C[h]	Dab + Tram (n=438) Pbo (n=432)	2.8 y	3-y: 58% vs 39% HR=0.47 [0.39–0.58] *P*<.001	NR[i] HR=0.51 [0.40–0.65] Nominal *P*<.001	3-y: 86% vs 77% HR=0.57 [0.42–0.79] *P*=.0006[j]	97% vs 88% 41% vs 14% 0.2% vs 0
BRIM8 NCT01667419 Maio et al,[44] 2018	III DB RCT	IIC, IIIA >1 mm, IIIB/C no IT[k]	Vem (n=250) Pbo (n=248)	2.5 y, 2.8 y[l]	2-y: 62% vs 53% HR=0.65 [0.50–0.85] *P*=.0013	2-y: 72% vs 65% HR=0.70 [0.52–0.96] *P*=.027	2-y: 90% vs 86% HR=0.76 [0.49–1.18] *P*=.2165	NR 57% vs 15% 0.4% vs 0

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

[a]Defined per AJCC 7th edition staging.

[b]Unless otherwise noted, Kaplan-Meier method was used to determine rates of RFS, DFS, DMFS, and OS.

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

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

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

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

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

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

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

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

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

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

Table 2. FDA-Approved Indications for Immune Checkpoint Inhibitor and BRAF/MEK Targeted Therapy in Cutaneous Melanoma

Agent	Treatment for Metastatic or Unresectable Disease	Adjuvant Therapy
Immune checkpoint inhibitors		
Ipilimumab[45]	Unresectable or metastatic melanoma	Cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy
Nivolumab[53]	Unresectable or metastatic melanoma	Melanoma with lymph node involvement or metastatic disease who have undergone complete resection
Pembrolizumab[116]	Unresectable or metastatic melanoma	Melanoma with involvement of lymph node(s) following complete resection
Nivolumab/ipilimumab[45,53]	Unresectable or metastatic melanoma	No FDA approval in this setting
BRAF targeted therapies		
Dabrafenib[150]	Unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test	No FDA approval in this setting
Vemurafenib[149]	Unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test	No FDA approval in this setting
BRAF/MEK inhibitor combinations		
Dabrafenib/trametinib[150,153]	Unresectable or metastatic melanoma with *BRAF* V600E or V600K mutations as detected by an FDA-approved test	Melanoma with *BRAF* V600E or V600K mutations, as detected by an FDA-approved test, and involvement of lymph node(s), following complete resection
Vemurafenib/cobimetinib[149,152]	Unresectable or metastatic melanoma with *BRAF* V600E mutation as detected by an FDA-approved test	No FDA approval in this setting
Encorafenib/binimetinib[151,154]	Unresectable or metastatic melanoma with a *BRAF* V600E or V600K mutation, as detected by an FDA-approved test	No FDA approval in this setting

Adjuvant ipilimumab was tested and FDA approved with a prolonged high-dose regimen: 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity.[19,45] In contrast, for treatment of unresectable or metastatic disease, the recommended ipilimumab dose is lower (3 mg/kg) and the treatment duration is shorter (every 3 weeks for a total of 4 doses).[45] Ipilimumab is associated with a variety of irAEs, and the frequency and severity of these toxicities have been shown to increase with dose.[46–49] A meta-analysis including 1,265 patients from 22 clinical trials found that the risk of developing an irAE (high grade) was 3-fold higher with ipilimumab 10 mg/kg versus 3 mg/kg.[47]

In EORTC 18071, grade 3–4 AEs were more common with ipilimumab versus placebo (Table 1).[20] Fatal ipilimumab-related AEs occurred in 5 patients (1%), and included colitis (n=3), myocarditis (n=1), and multiorgan failure with Guillain-Barré syndrome (n=1). Adverse events lead to discontinuation of treatment in 53% of patients who received high-dose adjuvant ipilimumab, compared with 5% of those who received placebo. An ongoing phase III randomized trial (ECOG 1609, NCT01274338) is testing whether adjuvant ipilimumab using the 3 mg/kg dosing will reduce toxicity without reducing clinical benefit. Preliminary results presented at ASCO suggest that RFS may be similar for 3 mg/kg and 10 mg/kg dosing, and that the lower dose may reduce the rate of grade 3–4 AEs.[50] This trial is also comparing adjuvant ipilimumab with adjuvant interferon to determine whether ipilimumab is more effective than the previous standard of care in the adjuvant setting, but data from the IFN alfa arm have not been reported.

Anti-PD-1 Monotherapy

Anti-PD-1 antibodies interfere with ligand binding by the T-cell surface receptor PD-1, resulting in enhanced T-cell activation.[51,52] Two PD-1 directed antibodies, nivolumab and pembrolizumab, have been tested as adjuvant treatment of resected melanoma in 2 phase III randomized trials (CheckMate 238 and KEYNOTE-054, respectively; Table 1).[21,22]

The CheckMate 238 study compared adjuvant nivolumab with adjuvant ipilimumab (10 mg/kg) in select patients

Table 3. NCCN Recommended Adjuvant Systemic Therapies

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

Abbreviations: NR, not recommended; cN+, clinically positive nodes (no in-transit or satellite metastases); CLND, complete lymph node dissection; dab/tram, combination dabrafenib/trametinib; ipi, high-dose ipilimumab (10 mg/kg); nivo, nivolumab; NR, not recommended; Obs, observation; pembro, pembrolizumab; SLN+, regional disease is limited to clinically occult nodal metastases; SLNB, sentinel lymph node biopsy; WLE, wide local excision of primary lesion.
[a]Clinical/pathologic stage as described in the NCCN Guidelines algorithm. Stages are defined according to AJCC 8th edition staging definitions. All nodal metastases must be pathologically confirmed. Initial presentation with stage IV disease or clinical recurrence should be confirmed pathologically whenever possible or if clinically indicated.
[b]Treatment within the context of a clinical trial is always a recommended option.
[c]Dabrafenib/trametinib is recommended only in patients with a *BRAF* V600 activating mutation.
[d]Category 1 for patients with AJCC 7th edition stage IIIB/C disease.
[e]Category 1 for patients with AJCC 7th rdition stage IIIA with SLN metastasis >1 mm or stage IIIB/C disease.
[f]Ipilimumab recommended only if patient has prior exposure to anti-PD-1 therapy.

with resected stage IIIB/C or stage IV (Table 1). At a median 19.5 months follow-up, nivolumab was associated with a clinically meaningful and statistically significant improvement in RFS and DMFS. The percent of patients experiencing grade 3–4 AEs was 30% lower in the nivolumab versus ipilimumab arm.[21] Further follow-up is needed to determine whether nivolumab favorably impacts OS compared with ipilimumab. Subgroup analyses also suggest that nivolumab significantly improves RFS (relative to ipilimumab) regardless of *BRAF* mutation status or PD-L1 expression status. Based on the demonstrated improvement in RFS, the FDA approved nivolumab for adjuvant treatment of resected nodal or metastatic melanoma (Table 2). Although the trial entry criteria required patients with stage IIIB/C disease (AJCC 7th edition) to have clinically detected lymph nodes and/or ulcerated primary, the FDA-approved indication is broader, including all patients with "lymph node involvement."

In the KEYNOTE-054 trial, pembrolizumab was compared with placebo in selected patients with resected stage III melanoma (Table 1). At a median follow-up of 1.2 years, pembrolizumab improved RFS and reduced risk of distant metastases; OS data were not mature at the time of the initial report.[22] Although the fraction of patients who experienced any grade of AE was similar across arms, high-grade AEs were somewhat more common in the pembrolizumab arm. Subgroup analyses suggest that improvement in RFS with pembrolizumab (relative to placebo) are not related to PD-L1 expression or *BRAF* mutation status.

Although there are no data from prospective randomized trials directly comparing adjuvant nivolumab versus pembrolizumab, the results from CheckMate 238 and KEYNOTE-054 suggest that these agents have similar efficacy and safety in the adjuvant setting.[21,22]

NCCN Recommendations for Adjuvant Immune Checkpoint Inhibitors

A summary of the NCCN recommended adjuvant systemic immune checkpoint inhibitor options and category of evidence and consensus for each of these recommendations are listed in Table 3 according to clinical/pathologic stage and primary treatment. Based on the results from CheckMate 238, the NCCN melanoma panel agrees that nivolumab should be listed as an adjuvant postoperative treatment option for patients with stage III/IV at presentation, as well as for patients with recurrent stage III/IV disease. Whereas the NCCN panel considers adjuvant nivolumab to be a reasonable option across a wider range of patients than were included in the CheckMate 238 trial, nivolumab is a category 1 option only in specific subgroups, based on the makeup of the study population and strength of data for specific subgroups. The NCCN panel agreed that results from CheckMate 238 provide high-level evidence that postoperative adjuvant nivolumab provides RFS benefit to patients who present or recur with clinically node-positive disease (Table 3). Because the trial excluded patients with stage IIIA disease (AJCC 7th edition staging), the panel is less confident about the

benefit of adjuvant nivolumab in patients whose nodal disease is detected by SLNB. The recommendation for adjuvant nivolumab is category 1 only for stage IIIB/C with lymph node metastases (AJCC 7th edition), used as selection criteria in the trial. Note that definitions of the stage III substages were significantly revised in the AJCC 8th edition update, such that some cases that were stage IIIB/C per the AJCC 7th edition would be reclassified as stage IIIA per the AJCC 8th edition, and vice versa. In addition, some cases that were stage IIIC per the AJCC 7th edition would be reclassified as stage IIID per the AJCC 8th edition. Results of trials based on AJCC 7th edition staging cannot be directly mapped to patients staged using the AJCC 8th edition, and all decisions should be informed by a thorough understanding of the probability of recurrence and the risks and potential benefits of a given adjuvant therapy. Although there may have been some patients with (resectable) in-transit disease in this trial, data from these patients were not reported separately, so adjuvant nivolumab is a category 2A recommendation in patients with satellite/in-transit disease (at initial presentation or recurrence), if complete excision to clear margins is achieved. The NCCN panel recommends referring to the FDA label for nivolumab for details on dosing and treatment administration.[53]

Based on the results of the KEYNOTE-054 trial, the NCCN panel recommends pembrolizumab as an adjuvant therapy option for patients with stage III disease (at presentation or recurrence) (Table 3). Similar to the situation with nivolumab, the NCCN panel considers adjuvant pembrolizumab to be a reasonable option across a wider range of stage III patients than were included in the KEYNOTE-054, but it is a category 1 option only in specific subgroups (Table 3). The NCCN panel agreed that the results from KEYNOTE-054 support adjuvant pembrolizumab as a category 1 option for patients with clinically detected nodal metastases. For patients with clinically occult nodal disease, the category 1 recommendation is limited to the subgroup of patients included in the trial: stage IIIA with at least 1 nodal metastasis >1 mm or stage IIIB/C, per AJCC 7th edition staging definitions. Patients with in-transit metastases were excluded from this trial, so adjuvant pembrolizumab is a category 2A option in this setting.

Although patients with stage IV disease were not included in the KEYNOTE-054 trial, the NCCN panel included adjuvant pembrolizumab as a category 2A option for resected stage IV disease. Because all the prospective randomized trial data thus far—both in the adjuvant setting and in the treatment of unresectable or distant metastatic melanoma—indicate that pembrolizumab and nivolumab are very similar in terms of efficacy and safety, the NCCN panel voted to recommend pembrolizumab in all the adjuvant settings where nivolumab was recommended (Table 3).

Although results from EORTC 18071 showed that adjuvant high-dose ipilimumab improved RFS, DMFS, and OS compared with placebo, results from CheckMate 238 showed that adjuvant nivolumab improved RFS compared with high-dose ipilimumab with a better safety profile (Table 1). Although, in contrast to adjuvant high-dose ipilimumab, the impact of adjuvant anti-PD-1 therapy on OS is not yet reported, the panel considered the relative difference in toxicity to be more important in the adjuvant setting. Moreover, as prospective randomized trials have shown anti-PD-1 therapy to be associated with better OS compared with ipilimumab in patients with unresectable/distant metastatic disease,[54,55] it is reasonable to extrapolate this observation into the adjuvant setting. Although not all the trials supporting anti-PD-1 therapy and BRAF-targeted therapy as adjuvant treatment options compared these agents to ipilimumab, the NCCN Melanoma Panel considers these agents to be more effective and better tolerated than ipilimumab, and therefore no longer recommends ipilimumab for adjuvant treatment (following resection) for patients with stage III disease at presentation. Ipilimumab is *no longer* listed among the options for first-line adjuvant systemic therapy for stage III disease shown on ME-4 (page 368), ME-5 (page 369), and ME-7 (page 370; Table 3).

For patients with a nodal recurrence after previous exposure to an anti-PD-1 agent, repeat exposure to adjuvant nivolumab or pembrolizumab may be less effective. This is a clinical scenario where ipilimumab remains an adjuvant treatment option (Table 3; ME-14/15; available online, in these guidelines, at NCCN.org). Based on similar logic, the NCCN panel voted to include adjuvant ipilimumab as an option for patients with resected stage IV disease who have prior exposure to anti-PD-1 agents (Table 3; ME-16, page 371). The preferred ipilimumab dose in the adjuvant setting varies across NCCN Institutions because although the efficacy of ipilimumab for adjuvant treatment was demonstrated in EORTC 18071 using the high-dose (10 mg/kg), the lower dose (3 mg/kg) is safer, and preliminary ECOG 1609 data presented at ASCO 2017 suggest that the lower dose may be equally effective in the adjuvant setting.[50] At present, this adjuvant ipilimumab dose reduction represents what the panel felt was a prudent but not yet evidence-based extrapolation of data derived from trials of its use in other settings.

BRAF Targeted Therapy

BRAF-targeted therapy has been tested as adjuvant treatment of resected melanoma in 2 prospective double-blind randomized controlled trials, COMBI-AD

and BRIM8 (Table 1).[23,44] COMBI-AD showed that in select patients with resected stage III disease and *BRAF* V600 E/K mutation, adjuvant treatment with the BRAF/MEK inhibitor combination dabrafenib/trametinib improved RFS and reduced risk of distant metastasis, albeit with a higher risk of toxicity (as expected).[23] OS rate was higher with dabrafenib/trametinib versus placebo, but the *P* value (*P*=.0006) did not meet the prespecified interim boundary (Table 1). The trial included patients with resected AJCC 7th edition stage IIIA who had at least 1 lymph node metastasis >1 mm, stage IIIB, or stage IIIC. Subgroup analyses showed RFS was significantly better with dabrafenib/trametinib for patients with *BRAF* V600E, and likely also improves RFS for patients with the less common *BRAF* V600K mutation. Based on results from COMBI-AD, dabrafenib/trametinib combination therapy was FDA approved as adjuvant therapy for patients with *BRAF* V600E/K mutations. Whereas COMBI-AD entry criteria required patients with stage IIIA (AJCC 7th edition) to have at least 1 lymph node metastasis >1 mm, the FDA-approved indication was broader, including all patients with lymph node involvement and complete resection (Table 2).

BRIM8 showed that in select patients with resected AJCC 7th edition stage IIC/III disease and *BRAF* V600 mutation, adjuvant treatment with the BRAF inhibitor vemurafenib monotherapy improved disease-free survival (DFS) and possibly DMFS compared with placebo (Table 1).[44] The effect on OS was not statistically significant, but these data remain immature. Patients with stage III disease in this trial were restricted to those who had AJCC 7th edition stage IIIA with at least 1 node with diameter >1 mm, or stage IIIB/C without in-transit metastases (Table 1). Given the improved efficacy/safety profile of BRAF/MEK inhibitor combination therapy compared with BRAF inhibitor monotherapy,[39,40,43] vemurafenib monotherapy is not FDA approved for adjuvant treatment of melanoma (Table 2).

NCCN Recommendations for BRAF-Targeted Adjuvant Therapy

Based on the results from the COMBI-AD trial, adjuvant dabrafenib/trametinib combination therapy is a recommended option for patients with resected stage III or recurrent disease and who harbor a *BRAF* V600 activating mutation (Table 3). Dabrafenib/trametinib is an adjuvant treatment option for all patients with stage III disease, even those categories of patients that were not included in the trial. The NCCN panel agreed that the data from the COMBI-AD trial provide high-level evidence that adjuvant dabrafenib/trametinib provide clinical benefit in patients with nodal metastases clinically detected at initial presentation or recurrence (following complete resection and CLND). However, among patients whose regional disease consists solely of clinically occult nodal metastases, the NCCN category 1 recommendation is limited to those whose extent of disease matches study entry criteria: stage IIIA with at least 1 nodal metastasis >1 mm or stage IIIB/C, as defined by AJCC 7th edition staging. Although COMBI-AD did include patients with in-transit metastases, results from these patients were not reported separately, so the adjuvant dabrafenib/trametinib is a category 2A option for patients with satellite/in-transit disease (if completely excised to clear margins). As the COMBI-AD trial excluded patients with distant metastases, dabrafenib/trametinib is not a recommended adjuvant treatment option for resected stage IV disease.

Although BRIM8 showed that adjuvant vemurafenib improved RFS and lowered risk of distant metastases relative to placebo, vemurafenib is not an FDA-approved adjuvant treatment option, and is not recommended by the NCCN panel.

Neoadjuvant Systemic Therapy

Data from pilot studies and phase I/II trials have shown promising results for use of BRAF-targeted therapies and immune checkpoint inhibitors as neoadjuvant treatment of resectable stage III–IV melanoma.[56–61] There are a number of ongoing trials testing neoadjuvant therapies for melanoma (ClinicalTrials.gov identifiers: NCT02858921, NCT03005639, NCT02231775, NCT02036086, NCT01972347, NCT02303951, NCT02306850, NCT03698019, NCT03618641, NCT03554083, NCT03259425, NCT02519322, NCT02434354, NCT02339324, NCT02211131).

NCCN Recommendations for Neoadjuvant Systemic Therapy

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

Treatment of Unresectable Stage III or Distant Metastatic Disease (Stage IV)

Systemic Therapy for Advanced Melanoma

The therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents that have demonstrated better efficacy than traditional chemotherapy. The first generation of novel targeted and immunotherapy agents (ie, vemurafenib, dabrafenib, ipilimumab) demonstrated significantly improved response rates and outcomes compared with

conventional therapies. Subsequently, a number of ongoing or recently completed phase II and phase III trials testing new immunotherapies, targeted therapies, and combination regimens have yielded noteworthy results.[32–36,38–40,43,54,55,62–71] Second and emerging third generations of effective agents and combination regimens are now available for treatment of advanced unresectable or metastatic melanoma.

Immune Checkpoint Inhibitors

The immune system may be capable of identifying and destroying certain malignant cells, a process called immunosurveillance. Conditions or events that compromise the immune system can lead to cancer cells escaping immunosurveillance.[72–74] Once cancer cells have escaped immunosurveillance and have begun to proliferate, their genetic and phenotypic plasticity enables them to develop additional mechanisms by which the nascent tumor can evade, thwart, or even exploit the immune system.[72–74] Immunotherapies are aimed at augmenting the immune response to overcome or circumvent the immune evasion mechanisms used by cancer cells and tumors. Some of the most effective immunotherapies target immune checkpoints—often exploited by cancers to decrease immune activity. For example, activation of T helper cells upon binding to antigens on the antigen-presenting cell (APC) can be modulated by other receptor-ligand interactions between the 2 cells. CTLA-4 and PD-1 are 2 examples of receptors on T-cells that upon ligand binding trigger a signaling cascade that inhibits T-cell activation, limiting the immune response.[75–78] Antibodies against these receptors (eg, ipilimumab, nivolumab, pembrolizumab) prevent receptor-ligand interaction, removing the inhibition of T-cell activation and "releasing the brake" on the immune response.[51,52,79] The importance of this science has recently been recognized by the awarding of the 2018 Nobel Prize in Medicine to James Allison and Tasuku Honjo for their research on CTLA-4 and PD-1.

Ipilimumab

Ipilimumab is a monoclonal antibody directed against the immune checkpoint receptor CTLA-4. Two phase III trials in patients with unresectable stage III or stage IV melanoma support the use of ipilimumab for advanced disease (Table 4). Results from these trials showed that ipilimumab improved response rates, response duration, PFS, and OS in patients with previously treated or previously untreated advanced disease.[28,29] Most importantly, extended follow-up showed that ipilimumab resulted in long-term survival in approximately 20% of patients (5-year OS, 18% vs 9% for dacarbazine),[80] consistent with findings from phase II trials.[81–83] Safety results from these trials showed that ipilimumab is associated with a substantial risk of irAEs, including grade 3–4 events (Table 4) and drug-related deaths (7 in CA184-002).[28] Even higher rates of grade 3–4 irAEs were observed in patients treated with ipilimumab in CA184-024 (Table 4), possibly due to the high dose used (10 mg/kg), or due to combination therapy with dacarbazine, or both.[29] Combination therapy with ipilimumab and dacarbazine therefore is not used in clinical practice, and the FDA-recommended dose of ipilimumab is 3 mg/kg rather than 10 mg/kg.[45] Results from CA184-169, a phase III randomized double-blind trial comparing ipilimumab 10 mg/kg dosing with 3 mg/kg, showed that the higher dose improved OS but was also associated with dramatically higher rates of treatment-related AEs (Table 4).[84] Immune-related AEs associated with ipilimumab and other immune checkpoint inhibitor regimens are detailed in the "Toxicity of Immune Checkpoint Inhibitors" section (page 385).

Given that treatment options may be limited for heavily pretreated patients who have progressed after immune checkpoint inhibitor therapy, it is noteworthy that reinduction therapy with ipilimumab was administered to a small number of patients in CA180-002 who had progressed after showing initial clinical benefit (responses or stable disease [SD] lasting ≥3 months). Disease control (complete response [CR], partial response [PR], or SD) was achieved after ipilimumab reinduction in most of these patients (20/31).[28,85] The frequency and types of ipilimumab-related irAEs seemed similar for reinduction as for initial treatment, and patients who experienced toxicities during the initial round of therapy did not necessarily experience the same irAEs upon reinduction.[85]

Anti-PD-1 Agents

While anti-CTLA 4 therapy appears to interfere primarily with the feedback mechanism at the interface between T cells and antigen-presenting dendritic cells, anti-PD-1 inhibitors are thought to interfere primarily with the feedback mechanism at the interface of T cells and tumor cells.[86]

Anti-PD-1 Agents: Pembrolizumab

Randomized trials in patients with unresectable stage III or stage IV metastatic disease have shown that pembrolizumab (monotherapy), like nivolumab, improves response and PFS compared with chemotherapy or ipilimumab (monotherapy)-(Table 5).[32,33,55,69] Keynote-002 compared pembrolizumab with investigators' choice of chemotherapy in patients with unresectable stage III or stage IV melanoma who had previously progressed on ipilimumab, and if *BRAF* V600 mutation positive, also progressed on a BRAF inhibitor.[32] More than

Table 4. Ipilimumab Trials in Advanced Melanoma[a]

Trial			Patients			Efficacy Results[b]						
Name and References	Phase Design	Median Follow-up, mo	Tx Naive	CNS Mets	Treatment Arms	Response Rate		PFS Median (mo)		OS Median (mo)		Grade 3–4 irAEs[c]
CA184-002 NCT00094653[28]	III RDB	21.0 27.8 17.2	0%[d]	12%[e]	Ipi + gp100 (n=403) Ipi (n=137) gp100 (n=136)	6% 11% 2%	P=.04 P=.001	2.8 2.9 2.8	P<.05[f] P<.001[f]	10.0 10.1 6.4	P<.001 P=.003	10%–15% 3%
CA184-024 NCT00324155[29,80]	III RDB	Min 36.6	100%	0%	DTIC + ipi (n=250) DTIC + pbo (n=252)	15% 10%	P=.09	ND[g] ND[g]	P=.0006[f]	11.2 9.1	P<.001	38% 4%
CA184-169 NCT01515189[84]	III RDB	14.5 11.2	44%[d] 43%[d]	18%[e] 17%[e]	HD-ipi (n=365) Ipi (n=362)	15% 12%		2.8 2.8	P=.16	15.7 11.5	P=.04	30% 14%

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

[a]Unresectable stage III or stage IV melanoma.

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

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

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

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

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

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

Table 5. Pembrolizumab Trials in Advanced Melanoma[a]

Name and References	Trial: Phase Design	Trial: Median Follow-up, mo	Patients: Tx Naive	Patients: Brain Mets[b]	Treatment Arms	Efficacy Results[c]: Response Rate	Efficacy Results[c]: PFS 2-year Rate	Efficacy Results[c]: OS 2-year Rate	Grade 3–4 Tx-Related AEs[d]
KEYNOTE-002 NCT01704287[32,69]	II R, OL	28	None[e]	–	Pembro 2 mg/kg Q3W (n=180) Pembro 10 mg/kg Q3W (n=181) Chemo (n=179)	22% 28% 4%	*P*<.0001[f] *P*<.0001	16% 22% <1%	*P*<.0001 *P*<.0001	36% 38% 30%	*P*=.117[f] *P*=.011	14% 16%[g] 26%
KEYNOTE-006 NCT01866319[33,55]	III R, OL	22.9	34%[h]	9%	Pembro 10 mg/kg Q2W (n=279) Pembro 10 mg/kg Q3W (n=277) Ipi 3 mg/kg Q3W x 4 doses (n=278)	37% 36% 13%	*P*<.001[i] *P*<.001	31% 28% 14%	*P*<.0001[i] *P*<.0001	55% 55% 43%	*P*=.0009[i] *P*=.0008	17% 17% 20%

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

[a]Unresectable stage III or stage IV melanoma.

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

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

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

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

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

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

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

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

70% of patients in this trial had received 2 or more prior systemic therapies. Long-term follow-up (median, 28 months) in the Keynote-002 trial showed that compared with chemotherapy, pembrolizumab provided higher rates and durations of response and was associated with long-lasting improvements in PFS (Table 5).[69] The trend toward improved OS was not statistically significant, however, even after adjustment for crossover.[69] Both the poor OS (compared with later trials testing pembrolizumab, see Table 5) and the failure to significantly improve OS compared with chemotherapy may be partly explained by the fact that patients in Keynote-002 were heavily pretreated.[32,69] Keynote-002 results showed that the rates of treatment-related AEs were somewhat lower with pembrolizumab compared with chemotherapy, although the only fatal treatment-related AE occurred in a patient treated with pembrolizumab, and immune-related AEs were of course largely limited to the pembrolizumab arms.[69] Compliance, global health status, and health-related quality of life were better with pembrolizumab compared with chemotherapy.[87]

Results from KEYNOTE-006 showed that in patients with one or fewer prior systemic therapies for advanced disease (and no prior immune checkpoint inhibitors), pembrolizumab improved response rate, PFS, and OS compared with ipilimumab (Table 5).[33,55] Long-term follow-up showed that whereas both pembrolizumab and ipilimumab provided extremely long-lived responses, pembrolizumab provided long-term improvement in PFS and OS compared with ipilimumab monotherapy (Table 5).[55,88] Post-hoc subanalyses after long-term follow up (median of 33.9 months) showed that compared with ipilimumab, pembrolizumab was associated with improvement in long-term PFS and OS for both patients who had received one prior systemic therapy and for those previously untreated.[89]

Although initial reports of KEYNOTE-006 showed lower rates of treatment-related toxicities with pembrolizumab compared with ipilimumab, after long-term follow-up, the cumulative rates of treatment-related toxicities were similar across treatment arms.[33,55] Toxicity rates were higher with ipilimumab during the first 12 weeks of study treatment, but the frequency of new AEs tapered off after the completion of the ipilimumab regimen (which consisted of a maximum of 4 cycles) around 12 weeks.[55] Although the rate of new AEs was lower with pembrolizumab during the first 12 weeks on study, new AEs continued to develop in the pembrolizumab arm throughout the study period (beyond 12 weeks) as patients continued to receive active treatment (no prespecified maximum treatment duration).[55]

Results of KEYNOTE-006 support the recommendation that pembrolizumab should be considered as

first-line therapy in patients with unresectable or distant metastatic disease.

Anti-PD-1 Agents: Kinetics of Response to Pembrolizumab

In clinical trials, the median time to response for pembrolizumab of approximately 3 months reflects time of the first tumor response assessment (12 weeks), similar to ipilimumab and nivolumab and similar to chemotherapy.[32,33,90,91] Long-term follow-up from several studies has shown that late responses to pembrolizumab can be observed more than a year after the start of treatment, and that initial PRs may become CRs with time.[32,33,69,89,91] A pooled analysis of cohorts from KEYNOTE-001 with long-term follow-up (median 43 months) showed that 16% of patients achieved CR, with median time to CR of 12 months, ranging from 3–36 months.[91]

Across trials long-term follow-up has shown that responses to pembrolizumab are very long-lived, with median duration ranging from 23 months (2 mg/kg Q3W arm in Keynote-002) to much longer (eg, not reached even after 33.9 months follow-up in KEYNOTE-006).[31,69,89,91] In contrast, median duration of response was 6.8 months for patients treated with chemotherapy in the KEYNOTE-002 trial.[69] Pooled analysis of Keynote-001 cohorts with long-term follow-up (median, 43 months) showed that although CRs to pembrolizumab took some time to develop, they were highly durable (88% of CRs persisting after a median follow-up time of 30 months from the first declaration of CR; 91% DFS 24 months after CR), even among patients who discontinued pembrolizumab.[91]

Anti-PD-1 Agents: Nivolumab

Checkmate 037 compared nivolumab versus investigator's choice chemotherapy in patients with unresectable stage III or stage IV melanoma who had previously progressed on ipilimumab, and if *BRAF* V600 mutation positive, also progressed on a BRAF inhibitor.[62] Over 70% of patients in this trial had received 2 or more prior systemic therapies. Results from Checkmate 037 show that nivolumab improved response rate and duration compared with chemotherapy (Table 6). However, after approximately 2 years follow-up, the improvement in response did not translate into improved PFS or OS (Table 6).[36,62] Safety results suggest that nivolumab may be better tolerated than chemotherapy in heavily pretreated patients with advanced disease (Table 6).[36,62]

Two subsequent phase III clinical trials in previously untreated patients have demonstrated nivolumab efficacy in unresectable stage III or stage IV melanoma (Table 6). As expected, the response rates to nivolumab in previously untreated patients in Checkmate 066 and 067 were higher than those seen in patients with prior systemic therapy for advanced disease treated in Checkmate 037 (Table 6). Results from Checkmate 066 showed that nivolumab improved response rate, PFS, and OS compared with chemotherapy.[66,70] The percent of grade 3-4 treatment-related AEs was initially lower with nivolumab compared with chemotherapy (12% vs 18%),[66] but longer follow-up showed that treatment-related AEs continued to develop in the nivolumab arm, diminishing the difference between the two arms (Table 6).[70] It is important to point out, however, that due to shorter time to progression, patients in the chemotherapy arm had shorter treatment duration than those in the nivolumab arm. Remarkably, the survival curve suggests that nivolumab may lead to long-term survival in up to 40% of patients.[70] Results from Checkmate 067 showed that nivolumab (monotherapy) improved response rate, PFS and OS compared with ipilimumab (monotherapy) (Table 6).[34,54,71] Although initial reports showed lower toxicity with nivolumab compared with ipilimumab (grade 3–4 treatment-related AEs for nivolumab vs ipilimumab: 16% vs 27%),[34] longer follow-up showed that treatment-related AEs continued to develop in the nivolumab arm, reducing the difference between arms (Table 6).[71] Analysis of Checkmate 067 results also showed that PFS and OS were similar for patients who discontinued nivolumab due to toxicity and patients who continued treatment.[71]

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

Anti-PD-1 Agents: Kinetics of Response to Nivolumab

Across trials the apparent median time to response for nivolumab closely reflects the time of the first response assessment (9 or 12 weeks),[34,36,62,66,68] similar to chemotherapy, ipilimumab, and pembrolizumab.[28,32,33] Initial analyses of Checkmate 037, 066, and 067 showed lower rates of CR than were reported in the final analyses after longer follow-up.[34,36,54,62,66,70,71] Similar to pembrolizumab, late CRs to nivolumab can be seen more than a year after the start of treatment. Across trials responses to nivolumab tend to be very long-lived, with median duration ranging from 31.9 months (Checkmate 037) to much longer (eg, not reached even after 38.4 months minimum follow-up in Checkmate 066).[35,36,54,70,71] In contrast, duration of response was much shorter in chemotherapy control arms (median 12.8 months in CheckMate 037, median 6.0 months in Checkmate 066).[36,70] Across trials, responses to nivolumab tend to persist after discontinuation of treatment.[35,36,62,68,70]

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

CTLA-4 and PD-1 inhibitor combination therapies have been investigated in a number of trials in unresectable stage III or stage IV melanoma (eg, CA209-004, Checkmate

Table 6. Nivolumab Trials in Advanced Melanoma[a]

Trial			Patients			Efficacy Results[c]						
Name and References	Phase Design	Median Follow-up (mo)	Tx Naive	CNS Mets[b]	Treatment Arms	Response Rate		Median PFS (mo)		Median OS (mo)		Grade 3–4 Tx-Related AEs[d]
CheckMate 037 NCT01721746[36,62]	III R, OL	~24	None[e]	20% 14%	Nivo (n=272) Chemo (n=133)	27% 10%		3.1 3.7	NS[f]	15.7 14.4	*P*=.716	14% 34%
CheckMate 066 NCT01721772[66,70]	III RDB	38[g] 39[g]	100%	3.6%	Nivo (n=210) DTIC (n=208)	43% 14%	*P*<.001	5.1 2.2	*P*<.001	37.5 11.2	*P*<.001	15% 18%
CheckMate 067 NCT01844505[34,54,71]	III RDB	47	100%	3.6%	Nivo + ipi, then nivo (n=314)	58%	*P*<.0001[h]	11.5	*P*<.0001[h]	NR	*P*<.0001[h]	59%
		36			Nivo (n=316)	45%	*P*<.0001	6.9	*P*<.0001	36.9	*P*<.0001	22%
		19			Ipi (n=315)	19%		2.9		19.9		28%
CheckMate 069 NCT01927419[35,68]	II RDB	25	100%	3%[g]	Nivo + ipi, then nivo (n=95)	59%	*P*<.0001	NR	*P*<.0001	NR	*P*=.26	54%
					Ipi (n=47)	11%		3.0		NR		20%

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

[a]Unresectable stage III or stage IV melanoma.

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

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

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

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

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

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

[h]In Checkmate 067, objective response rates were higher with nivolumab/ipilimumab combination versus nivolumab monotherapy: 58% (95% CI, 52.6–63.8) vs 45% (95% CI, 39.1–50.3). Descriptive analysis suggest 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]).

064, Checkmate 067, Checkmate 069, Checkmate 204, NCT02731729, NCT02374242, Keynote-029).[34,68,92–98] Results from 2 randomized trials (Checkmate 067, Checkmate 069) demonstrated that the response rate with ipilimumab/nivolumab combination therapy was substantially higher than with ipilimumab alone (Table 6).[34,35,54,68,71] Both trials showed that PFS was substantially better with combination therapy compared with ipilimumab monotherapy (Table 6).[34,54,71] Checkmate 067 showed that OS was improved with combination therapy versus ipilimumab (Table 6), and these effects persisted through long-term follow-up. The 4-year survival rates in Checkmate 067 are 37% for ipilimumab/nivolumab, 31% for single-agent nivolumab, and 9% for single-agent ipilimumab.[71] In Checkmate 069, a smaller randomized phase II study, results after 25 months median follow-up showed a trend toward improved OS with combination therapy compared with ipilimumab (2-year rate: 63.8% [95% CI, 53.3–72.6] vs 53.6% [38.1–66.8] that was not statistically significant, although at the time of analysis median OS had not been reached in either arm (Table 6).[35,68]

Checkmate 067 included an arm of patients treated with nivolumab monotherapy, although it was not powered to compare results to patients treated with combination therapy.[34] Response rate was higher with nivolumab/ipilimumab combination therapy compared with nivolumab monotherapy (58% vs 45%), and descriptive analysis showed improved PFS (HR=0.79; 95% CI, 0.65–0.97).[71] A similar trend in OS did not reach statistical significance (Table 6, footnote h).[71] Subset analysis suggested that patients expressing high levels of PD-L1 expression treated with nivolumab monotherapy had a similar OS and PFS to patients treated with the more toxic combination therapy (See "Anti-PD-1 Therapy in Patient Subpopulations: PD-L1 Expression," next column).

Checkmate 067 and 069 also showed substantially increased toxicity with immune checkpoint inhibitor combination therapy versus monotherapy (Table 6). In both trials, combination therapy was associated with a much higher rate of discontinuation due to AEs.[34,99] A pooled analysis of these trials found that among patients treated with nivolumab/ipilimumab combination therapy, those who discontinued during the induction phase due to AEs had similar response rates, PFS, and OS as patients who did not discontinue early due to toxicity (but may have continued for other reasons).[100] There are ongoing clinical trials evaluating even lower doses of ipilimumab in combinations to mitigate the toxicity while still maintaining the synergy of the combination.[98,101,102]

Anti-CTLA-4/Anti-PD-1 Combination Therapy: Kinetics of Response

Combination therapy with ipilimumab and nivolumab is associated with improved response rate compared with ipilimumab monotherapy, but as for ipilimumab and nivolumab monotherapy, the apparent median times to response reflect the time to first response assessment (12 weeks).[34] As for nivolumab monotherapy, late CRs to combination therapy were seen more than a year after the start of treatment: the rate of CR nearly doubled (increased from 11.5% to 21%) between the first primary report (median follow-up ≈12 months) and the most recent analysis (median follow-up 47 months).[34,71] As for single-agent anti-PD-1 therapy, duration of responses were also long. In CheckMate 067 the median duration of response was 50.1 months for combination therapy and was not reached for single agent nivolumab after a minimum of 48 months follow-up.[71]

Anti-PD-1 Therapy in Patient Subpopulations: BRAF Mutation Status

Subgroup analyses in the Checkmate and KEYNOTE trials showed that patients with *BRAF* mutant tumors and those with *BRAF* wild-type tumors derived clinical benefit from anti-PD-1 therapy compared with controls (single-agent ipilimumab or chemotherapy).[32–34,54,55,62,66,69–71] Likewise, subgroup analyses in CheckMate 067 and 069 showed improved efficacy with nivolumab/ipilimumab combination therapy compared with ipilimumab monotherapy regardless of *BRAF* mutation status.[34,35,54,68,71]

Anti-PD-1 Therapy in Patient Subpopulations: PD-L1 Expression

To determine whether the PD-1 ligand (PD-L1) could be used to identify candidates for anti-PD-1 therapy, PD-L1 expression was assessed in tumor samples from patients in the CheckMate and KEYNOTE trials, and various expression level cutoffs were analyzed to see whether PD-L1 expression levels could be used as a biomarker to predict response to anti-PD-1 therapy.[34,62,66,68,89,103] Across trials, response rate, PFS, and OS for anti-PD-1 therapy tend to improve with increasing PD-L1 expression.[34,36,54,70,71,89,104] However, there were patients who experienced durable responses to anti-PD-1 therapy despite having little or no PD-L1 expression detected in their tumor samples.[34,36,54,66,71,89,104] Analysis of data from Checkpoint 067 showed that although nivolumab efficacy appeared to improve with increasing PD-L1 expression, time-dependent receiver operator characteristic (ROC) curves indicated that PD-L1 expression alone is an insufficient biomarker to predict OS among patients treated with nivolumab.[71] In trials comparing anti-PD-1 monotherapy to ipilimumab monotherapy, subgroup analyses by PD-L1 expression showed that while response rate, PFS, and OS are higher with anti-PD-1 monotherapy compared with ipilimumab monotherapy for most PD-L1 expression levels, these treatment-dependent differences are smaller

among patients with extremely low PD-L1 expression (<1% of cells showing membrane staining).[71,89] None of these analyses, however, were able to identify a PD-L1 expression threshold for selection of an anti-PD-1 agent versus other options.

Among patients treated with nivolumab plus ipilimumab combination therapy, response rate, PFS, and OS tend to increase with increasing PD-L1 expression level.[71,94] Similar to the results for nivolumab monotherapy, ROC curves in Checkmate 067 showed that PD-L1 alone is insufficient for predicting OS among patients treated with nivolumab/ipilimumab combination therapy.[71] Nivolumab/ipilimumab combination improved response rate and outcomes compared with ipilimumab monotherapy for all PD-L1 expression levels tested, including patients with very low PD-L1 expression.[71] Descriptive analyses showed that among patients with low PD-L1 expression, nivolumab/ipilimumab seems to improve outcomes relative to nivolumab monotherapy. Improvements in outcome with combination therapy versus nivolumab monotherapy were not apparent among patients with higher PD-L1 levels.[71] The apparent predictive/prognostic value of PD-L1 is limited by the expression assays and different PD-L1 thresholds across studies. At present, the expression of PD-1 should not be used to exclude patients from anti-PD-1 monotherapy, but may be helpful when choosing between anti-PD-1 monotherapy and ipilimumab/nivolumab combination therapy.

Sequence of Immune Checkpoint Inhibitors

Ongoing studies are aimed at determining the efficacy of sequential monotherapy with ipilimumab and PD-1 inhibitor. Preliminary results from a randomized phase II trial show increased toxicity but trends toward improved response rate and OS for patients treated with nivolumab followed by ipilimumab compared with patients who received these therapies in the reverse order.[92] Cross-trial comparison suggests that patients who have progressed on ipilimumab have lower response rates and poorer outcomes on anti-PD-1 agents compared with patients who have not had prior systemic therapy (Tables 5 and 6). Subgroup analyses of data from Keynote-001 and Keynote-006 suggest that pembrolizumab is more effective as a first-line agent than as a second-line agent, even among patients with no prior immune checkpoint inhibitor therapy.[31,89] A retrospective analysis showed responses to pembrolizumab in patients previously treated with ipilimumab is correlated with the patient's prior response to ipilimumab (duration of PFS).[105]

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

For a description of data supporting combination therapy with immune checkpoint inhibitors and intralesional injection of talimogene laherparepvec, see full NCCN Guidelines for Cutaneous Melanoma, available at NCCN.org.

Immune Checkpoint Inhibitor Administration

The ipilimumab treatment regimen of 3 mg/kg every 3 weeks for 4 doses in patients with unresectable or distant metastatic melanoma is well supported by clinical trial data and approved by the FDA.[28,29,45] Furthermore, this is the dose that is approved for use in combination with PD-1 blockade when clinically indicated.

For anti-PD-1 agents, however, there are fewer data to support the optimal dose and duration of treatment. Analyses of randomized cohorts in the KEYNOTE-001 phase I trial showed that there is no clinically meaningful difference in response rate, PFS, and OS for the 3 pembrolizumab regimens tested (2 mg/kg Q3W, 10 mg/kg Q3W, 10 mg/kg Q2W).[31,90] Results from Keynote-002 and Keynote-006 support this observation (Table 5). Dose-finding trials for nivolumab included patients with a variety of cancer types, and sample sizes for each of the dose levels tested in melanoma patients are too small to be sure of the best dose specifically for patients with melanoma.[106–113]

Table 7 summarizes the treatment dosing and duration used in the pivotal trials supporting anti-PD-1 agents for use in unresectable or metastatic melanoma, as well as the current FDA recommended dosing. For both nivolumab and pembrolizumab, the FDA recommended dosing no longer reflects the dosing used in the pivotal trials supporting use of these agents for unresectable or distant metastatic melanoma. Flat dosing regimens for both nivolumab and pembrolizumab were identified by pharmacokinetic models based on data on body weight, exposure, and toxicity from large populations pooled from many trials across a variety of tumor types.[110–112,114,115]

Although the product labels for nivolumab and pembrolizumab indicate that treatment should continue until disease progression or unacceptable toxicity,[53,116] the published trials allowed shorter or longer treatment in certain situations. As mentioned previously, long-term follow-up in trials testing anti-PD-1 agents (as monotherapy or in combination with ipilimumab) have shown that responses are very durable and often persist for years beyond treatment discontinuation.[70,71,91,117] Evidence is accumulating that although most responses to anti-PD-1 therapy develop within 6 months,[32,35,36,68,70,91] there is a notable fraction of responses that take a very long time to develop, and some patients may even experience progression (RECIST-defined) before responding.[32–34,36,54,55,62,66,69–71,89,91,118] Exploratory analyses of phase II/III trials testing nivolumab (Checkmate 037, 066, 067) reported that in highly selected patients who per

Table 7. Immune Checkpoint Inhibitor Treatment Regimens

	Dosing	Treatment Duration
Nivolumab		
CheckMate 066[66] CheckMate 067[34] CheckMate 037[62]	3 mg/kg Q2W	Until disease progression or unacceptable toxicity Patients who had clinical benefit could opt for treatment beyond progression, provided they had not experienced substantial AEs
FDA Prescribing information[53]	240 mg Q2W or 480 mg Q4W	Until disease progression or unacceptable toxicity
Pembrolizumab		
KEYNOTE-002[32]	2 mg/kg or 10 mg/kg Q3W	Until disease progression or unacceptable toxicity Patients with PD at 12-week scan could opt to continue until confirmation of PD at next scan
KEYNOTE-006[33]	10 mg/kg Q2W or Q3W	Until disease progression, unacceptable toxicity, or 24 months Patients with CR lasting ≥6 months could discontinue after an additional 2 treatments
FDA Prescribing information[116]	200 mg Q3W	Until disease progression or unacceptable toxicity
Ipilimumab/Nivolumab Combination		
CheckMate 067[34] CheckMate 069[68]	1 mg/kg nivo + 3 mg/kg ipi (same day), Q3W for 4 doses; then 3 mg/kg nivo monotherapy Q2W	Until disease progression or unacceptable toxicity Patients who had clinical benefit could opt for treatment beyond progression, provided they had not experienced substantial AEs
FDA Prescribing information[53]	1 mg/kg nivo + 3 mg/kg ipi (same day), Q3W for 4 doses; then 240 mg Q2W or 480 mg Q4W	Until disease progression or unacceptable toxicity

Abbreviations: CR, complete response; Ipi, ipilimumab; nivo, nivolumab; PD, progressive disease; Q2W, once every 2 weeks; Q3W, once every 3 weeks; Q4W, once every 4 weeks.

the investigators' discretion were allowed treatment of a limited period beyond progression, subsequent reduction in tumor burden was sometimes observed.[62,66,119] A pooled analysis of data from 8 clinical trials found that in patients receiving anti-PD-1 agents (either alone or in combination) treatment beyond RECIST-defined progression resulted in further reduction in tumor burden by 30% or more in 19% of patients, as well as improvement in OS for patients treated beyond progression versus those who discontinued treatment at the time of progression.[120] Other exploratory analyses of trials have shown that early discontinuation of anti-PD-1 therapy (ie, due to AEs) does not impact clinical outcomes,[71,100] and that responses can occur after discontinuation.[100] It is unclear whether treatment beyond progression was really responsible for the positive outcomes observed. Prospective randomized trials are needed to determine the duration of anti-PD1 treatment needed to optimize clinical benefit and minimize risk of toxicity.

Toxicity of Immune Checkpoint Inhibitors

Most of the treatment-related AEs associated with immune checkpoint inhibitors are autoimmune in nature. The array of immune-related toxicities associated with immune checkpoint inhibitors (across all cancer types), as well as recommendations for management of each, can be found in the NCCN Guidelines for Management of Immunotherapy-related Toxicities (available at NCCN.org). Table 8 lists types and rates for the most common toxicities seen in prospective randomized trials that compared immune checkpoint inhibitors in patients with unresectable stage III or stage IV cutaneous melanoma. Across all 3 immune checkpoint inhibitor options shown in Table 8 (ipilimumab, anti-PD-1 monotherapy, ipilimumab/nivolumab combination therapy), the most common AEs were cutaneous toxicities (rash, pruritus, maculopapular rash and vitiligo), gastrointestinal toxicities (diarrhea/colitis), and fatigue. Aside from these 3 types of toxicities, the most common high-grade toxicities observed in clinical trials are endocrinopathies (eg, hypophysitis, adrenal insufficiency, hypo- or hyperthyroidism), pancreatitis (elevated lipase and amylase), and hepatic AEs (eg, elevated ALT/AST, hepatitis).[45] Other less common but potentially life-threatening high-grade immune-related toxicities include nephritis, pneumonitis, and myocarditis. Management of these unusual

Table 8. Checkpoint Immunotherapies: Treatment-Related Toxicities[a]

Study	CheckMate 067 and 069[35,71]						KEYNOTE-006[33,55]			
Agent	Ipilimumab		Nivolumab[b]		Ipilimumab + Nivolumab		Ipilimumab		Pembrolizumab	
Grade	3–4	Any	3–4	Any	3–4	Any	3–5	Any	3–5	Any
All types	20–28	86–94	22	86	54–59	90–96	20[c]	73–74[c]	12–17[c]	76–80[c]
Diarrhea	6–11	***	3	**	10	*****	3[c]	**[c]	2–3[c]	**[c]
Colitis	2–8	*	1		8–13	**	6	*	3	
Nausea	1–2	**	0	*	1–2	***	<1[c]	*[c]	<1[c]	*[c]
Vomiting	<1	*	<1	*	1–2	**	0	*	<1	
Decreased appetite	<1	*	0	*	≤1	**	0	*	0	*
Rash	≤2	***	<1	**	3–4	****	≤1[c]	**[c]	0[c]	**[c]
Pruritus	<1	****	<1	**	1–2	****	<1[c]	***[c]	0[c]	**[c]
Maculopapular rash	<1	*	1	*	2–3	**	<1		<1	
Vitiligo	0[b]	*[b]	<1	*	0[b]	*	0		0	*
Fatigue	≤1	*****	1	****	4–5	****	1[c]	**[c]	≤1[c]	***[c]
Pyrexia	<1	*	0	*	1–3	**	0		0	
Arthralgia[b]	0[b]	*[b]	<1[b]	*	1	*[b]	≤1[c]	*[c]	<1[c]	*[c]
Myalgia	0	*	<1	*	<1	*	<1		<1	
Asthenia	1[b]	*[b]	<1	*	<1[b]	*[b]	1	*	<1	*
Headache	<1	*	0	*	1–2	*	0		0	
Dyspnea	0		<1	*	1–2	*	<1		<1	
Cough	0	*	1	*	0	*	0		0	
Abdominal pain	1–2	*	0	*	<1	*	0	*	0	
Chills	0	*	0		0	*	0		0	
Elevated ALT	≤2	*	1		9–11	***	1		<1	
Elevated AST	≤1	*	1		6–7	***	1		<1	
Hypophysitis	2–4	*	<1		2	*	1		<1	
Hypothyroidism	0	*	0	*	<1	**	0[c]	[c]	<1[c]	*[c]
Hyperthyroidism	0[b]		0		1[b]	*[b]	<1		0	
Elevated lipase	≤4	*	5	*	10–11	**	–	–	–	–
Elevated amylase	≤1		2	*	2–3	*	–	–	–	–
Pneumonitis	<1		<1		1–2	*	–	–	–	–
Creatinine increased	0		<1		≤1		0		0	

–, not reported

[a]Specific AEs listed occurred in ≥10% of patients for at least one checkpoint immunotherapy regimen. Shows percent of patients who experienced at least one AE of any grade, grade 3–4 or grade 3–5. For the any grade column, the percent of patients affected by specific AEs (any grade) was rounded to the nearest 10%, then assigned one asterisk (*) for every 10% of patients effected. Blank indicates that <5% of patients experienced the AE.

[b]Data available from only 1 of 2 trials.

[c]For KEYNOTE-006, unless otherwise noted data shown are from the first interim analysis based on median follow-up of 7.9 months. Footnote indicates data from a later report based on median 22.9 months follow-up. The later report did not include a complete AE listing.[55]

events is summarized in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities. Analysis of the WHO pharmacovigilance database, including patients treated with immune checkpoint inhibitors for any indication, found that for patients treated with anti-CTLA-4, colitis caused the most AE-related deaths, whereas AE-related deaths for anti-PD-1/PD-L1 agents were most often from pneumonitis, hepatitis, and neurotoxic effects.[121] AE-related deaths in patients treated with combination PD-1/CTLA-4 inhibitors were most frequently from colitis or any myocarditis.[121]

Although there are no data from prospective randomized trials directly comparing nivolumab versus pembrolizumab, these agents appear to have similar safety profiles (Table 8). Safety results from randomized phase II–III trials showed that combination

therapy with nivolumab and ipilimumab was associated with more toxicity than single-agent ipilimumab or nivolumab (Table 8).[34,35,68,71] Ipilimumab/nivolumab combination therapy increased the total number of patients with treatment-related AEs of any grade and notably increased the occurrence of grade 3–4 AEs (Table 8) and AEs leading to treatment discontinuation (40% for nivolumab/ipilimumab combination vs 13% for nivolumab monotherapy, 15% for ipilimumab monotherapy).[71] Table 8 shows that many of the common toxicities were more frequent or more often high-grade with combination ipilimumab plus anti-PD-1 regimens than with immune checkpoint inhibitor monotherapy. Although earlier reports suggested that anti-PD-1 monotherapy was associated with less toxicity than ipilimumab, these differences appear to be less significant with longer term follow-up (Table 8).[33–35,55,68,71]

Kinetics of Immune-Related Toxicities

Pooled analyses of data from prospective trials testing immune checkpoint inhibitors in patients with unresectable or distant metastatic melanoma show that time to onset and time to resolution differ across different types of AEs.[122,123] Most skin-related AEs manifest early, but risk of developing a cutaneous AE persists throughout treatment. Among high-grade AEs, gastrointestinal and hepatic toxicities tend to take a bit longer to develop (than cutaneous AEs), followed by pulmonary, endocrine, and renal AEs. Although these trends are clear, for many irAEs the ranges of time to onset are quite broad. Although uncommon, initial irAEs have been observed up to a year following initiation of treatment. Median time to resolution is similar for most types of common high-grade AEs, on the order of months, but endocrine AEs may not resolve. Up to 20% of high-grade cutaneous AEs also appear to persist indefinitely.[122,123] Analysis of the WHO pharmacovigilance database found that fatal AEs associated with immune checkpoint inhibitors (all indications) usually occurred within the first 2 months of treatment.[121]

BRAF-Targeted Therapies

Approximately half of patients with metastatic cutaneous melanoma harbor an activating mutation of BRAF, an intracellular signaling kinase in the MAPK pathway.[124–126] Most BRAF-activating mutations occurring in melanomas are at residue V600 (usually V600E but occasionally V600K or other substitutions).[125,127] BRAF inhibitors have been shown to have clinical activity in unresectable metastatic melanomas with *BRAF* V600 mutations. Coadministration of inhibitors of MEK, a signaling molecule downstream of BRAF, potentiates these effects. Efficacy and safety data from large randomized trials testing BRAF and MEK inhibitors have significantly impacted the recommended treatment options for patients with *BRAF*-mutation positive unresectable advanced melanoma.

For discussion of data on the efficacy of BRAF inhibitor monotherapy for the treatment of metastatic melanoma, see full NCCN Guidelines for Cutaneous Melanoma, available at NCCN.org.

BRAF/MEK Inhibitor Combination Therapy

Despite high initial response rates, half of the patients treated with BRAF-targeted monotherapies relapse within 6 months, due to development of drug resistance.[40,41,65,128–132] Alternate methods for targeting the MAP kinase pathway are being explored as options for overcoming resistance to BRAF inhibitor therapy. Trametinib, cobimetinib, and binimetinib are oral small-molecule inhibitors of MEK1 and MEK2, signaling molecules downstream of BRAF in the MAP kinase pathway. Results from a phase III randomized trial (NCT01245062) showed that, in patients with *BRAF*-mutated metastatic melanoma not previously treated with BRAF inhibitors, trametinib improves PFS and OS compared with chemotherapy.[133] Although trametinib response rate (22%) was significantly better than chemotherapy (8%, P=.01), it was lower than response rates for vemurafenib (48%, 53%) and dabrafenib (50%) from phase II–III trials.[37,41,128] Moreover, in an open-label, phase II study, trametinib failed to induce objective responses in 40 patients previously treated with a BRAF inhibitor.[134] Binimetinib, has also been shown to provide improved response rates and PFS compared with DTIC in a phase 3 randomized trial in patients with unresectable stage IIIC or stage IV melanoma with NRAS Q61R/K/L mutations.[135] Nonetheless, the ORR (15%) and PFS (median 2.8 months) for patients treated with binimetinib were poor compared with those for BRAF inhibitors tested in other trials.

Although MEK inhibitor monotherapy has limited utility for treating advanced metastatic melanoma, several phase III trials have now demonstrated that combination therapy with a BRAF and MEK inhibitor has better efficacy than BRAF inhibitor monotherapy for previously untreated unresectable or distant metastatic disease (Table 9).[39,40,43,132,136,137] When compared with either single-agent dabrafenib or single-agent vemurafenib, BRAF/MEK inhibitor combination therapy with dabrafenib and trametinib or vemurafenib plus cobimetinib improved response rate, duration of response, PFS, and OS.[39,40,43,132] A recent phase 3 randomized trial (COLUMBUS) showed that encorafenib, a BRAF inhibitor, when combined with the MEK inhibitor binimetinib, improves PFS and OS compared with vemurafenib monotherapy.[138,139] Patients in the COLUMBUS trial were treatment naïve or had progressed on or after previous first-line immunotherapy; no other prior therapies for locally advanced, unresectable, or metastatic

Table 9. BRAF/MEK Inhibitor Combination in Advanced Melanoma[a]: Key Trials

Trial			Patients				Efficacy Results[b]						
Name and References	Phase Design	Median follow-up (mo)	Prior BRAFi	Tx Naive	Brain Mets	Treatment Arms	Response Rate		Median PFS (mo)		Median OS (mo)		AEs Grade 3–4[c]
BRIM-7	Ib	26	0[d]	Some[d]	–[e]	Vem + cobi (n=63)	87%		13.8		31.2		78%
NCT01271803[141–143]	OL, dose escalation	8	100%[d]	0[d]		Vem + cobi (n=66)	15%		2.8		8.5		47%
NCT02296996[145]	II OL	6.8	100%[f]	0	68%	Dab + tram (n=25)	32%		4.9		NR		8%
NCT01072175[67]	I/II	35.3	100%[g]	0	23%	Dab + tram (n=26)	15%		3.6		10.0		61%
	OL	27.4	100%[g]	0	9%	Dab + tram (n=45)	13%		3.6		11.8		44%
NCT01072175 Part C[131,166]	II R	66.5	0	Some[h]	4%[e]	Dab (150 mg BID) + tram (2 mg QD) (n=54)	76%	P=0.03	9.4	P<0.001	25.0		67%
			0		13%[e]	Dab (150 mg BID) + tram (1 mg QD) (n=54)	50%	P=0.77	9.2	P=0.006	22.5		54%
			0		7%[e]	Dab (150 mg BID) (n=54)	54%		5.8		20.2		47%
NCT01619774[144]	II	5.9	100%[g]	0	–[e]	Dab + tram (n=23)	10%		3.0		10.2		71%
COMBI-d	III	20	0	100%	–[e]	Dab + tram (n=211)	69%	P=0.0014	11.0	P=0.0004	25.1	P=0.0107	48%[i]
NCT01584648[39,136]	RDB	16	0			Dab + pbo (n=212)	53%		8.8		18.7		50%[i]
COMBI-v	III	11	0	100%	–[e]	Dab + tram (n=352)	64%	P<0.001	11.4	P<0.001	NR	P=0.005	52%
NCT01597908[40]	R, OL	10	0			Vem (n=352)	51%		7.3		17.2		63%
Co-BRIM	III	14.2 (response, PFS)	0	100%	<1%[e]	Vem + cobi (n=247)	70%	P<0.0001	12.3	P<0.0001	22.3	P=0.005	75%
NCT01689519[43,132,137]	RDB	18.5 (OS, AEs)	0		<1%[e]	Vem + pbo (n=248)	50%		7.2		17.4		61%
COLUMBUS	III	32.1 (PFS)	0	70%[j]	5%[e]	Encor + bini (n=192)	64%		14.9	P<0.0001[k]	33.6	P<0.0001[k]	64%
NCT01909453[138,139]	R, OL	36.8 (OS)	0	70%[j]	–[e]	Encor (n=194)	52%		9.6	P=0.0038[k]	23.5	P=0.033[k]	67%
			0	70%[j]	2%[e]	Vem (n=191)	41%		7.3		16.9		66%

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

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

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

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

[d]BRIM-7 included a cohort of patients who had recently progressed on vemurafenib (n=66) and a cohort of patients with no prior BRAF inhibitor (n=63). Each may have had other types of prior systemic therapy. For the latter, the number without any prior treatment was not reported.

[e]Patients with active brain metastases were excluded from the trial. Treated stable brain metastases were allowed.

[f]In NCT02296996, patients were required to have progressed on prior BRAF inhibitor therapy (or BRAF/MEK inhibitor combination therapy) and to have progressed on prior anti-CTLA-4 or anti-PD-1 checkpoint inhibitor therapy.

[g]Johnson 2014[67] 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.

[h]In Part C of NCT01072175, all patients had no prior BRAF or MEK inhibitor treatment, but some had prior chemotherapy (13% vs 28% vs 22%) and some had prior immunotherapy (24% vs 30% vs 15%). The number with no prior systemic therapy was not reported.

[i]Based on analysis after ≥36-month follow-up for all living patients.

[j]In COLUMBUS, 30% of patients in each arm had prior systemic immunotherapy, mostly IFN or interleukins. Other types of prior systemic therapy were not allowed.

[k]In COLUMBUS, encorafenib/binimetinib combination therapy versus encorafenib monotherapy did not result in significantly different PFS (HR=0.75 [95% CI, 0.56–1.00]; P=.050) or OS (HR=0.81 [95% CI, 0.61–1.06]; P=.12).

melanoma were allowed. This trial also compared encorafenib/binimetinib combination therapy versus encorafenib monotherapy, but the improvements in PFS and OS did not reach statistical significance. Although across trials of patients with previously untreated metastatic disease, vemurafenib monotherapy and dabrafenib monotherapy have resulted in roughly similar response rates and PFS,[37–43,132,136,137,140] results from the COLUMBUS trial showed that encorafenib monotherapy improved PFS and OS compared with vemurafenib monotherapy.[138,139]

The efficacy of BRAF/MEK inhibitor combination therapy in patients with previously treated advanced melanoma is a topic of ongoing research. Results from phase I/II studies (Table 9) showed that in patients who have received previous BRAF inhibitor treatment, subsequent BRAF/MEK inhibitor combination therapy was associated with a relatively poor response rate, PFS, and OS, compared with patients who had not received prior BRAF inhibitor treatment.[67,141–145] Likewise, although encorafenib improved response rate and PFS compared with vemurafenib in patients with no prior BRAF inhibitor treatment (Table 9), data from a phase 1 trial suggest that patients with prior dabrafenib or vemurafenib treatment still have fairly low response rates and poor PFS when treated with encorafenib.[146] However, emerging data suggest that resistance to BRAF-targeted therapy may not be as irreversible as previously thought. A subset analysis in one of these studies (NCT01072175) showed that patients who had rapidly progressed on first-line BRAF inhibitor therapy (time to progression <6 months) derived little or no clinical benefit from second-line BRAF/MEK inhibitor combination therapy compared with patients whose resistance to first-line BRAF inhibitor monotherapy occurred at ≥6 months (response rate, 0% vs 26%; median PFS, 1.8 months vs 3.9 months; P=.018).[67] One single-arm phase II study (NCT02296996) that restricted enrollment to patients who had previously progressed on BRAF-targeted therapy, and progressed on anti-CTLA-4 or anti-PD-1, and had least 12 weeks since finishing their last BRAF-targeted treatment, found that response rate was relatively high (32%) compared with other prospective studies that tested BRAF/MEK inhibitor therapy in patients who previously progressed on BRAF-targeted therapy (response rate 10%–15% in BRIM-7, NCT01072175, NCT01619774; see Table 9).[67,144,145] Some of the patients who responded to rechallenge had previously progressed on BRAF/MEK inhibitor combination therapy.[145] These results from NCT01072175 and NCT02296996 suggest that resistance to BRAF-targeted therapy may be reversible, at least in some patients. Identification of the best candidates for retreatment is a topic of ongoing research.

Across trials, the apparent time to response for all BRAF/MEK inhibitor combinations reflects the time to first tumor response assessment (6 weeks in BRIM-7, 8 weeks in other trials).[43,131,138,141] Results from multiple randomized trials suggest that BRAF/MEK inhibitor combination therapy may improve duration of response compared with BRAF inhibitor monotherapy, although the magnitude of this effect varies, with increases in median duration of response ranging from 2–6 months.[40,131,132,136,139]

BRAF and MEK Inhibitor Safety

Table 10 summarizes the safety data from phase III trials comparing BRAF/MEK inhibitor combination therapy to BRAF inhibitor monotherapy. The risk of toxicity (all grade, grade 3–5) was similar for BRAF/MEK inhibitor combination therapy compared with single-agent BRAF inhibitor therapy, and BRAF inhibitor monotherapies (vemurafenib, dabrafenib, encorafenib) and BRAF/MEK inhibitor combinations (dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib), were associated with high rates of flu-like symptoms: pyrexia and chills, fatigue and asthenia, headache, various types of musculoskeletal aches and pains (eg, arthralgia, myalgia), and gastrointestinal upset (diarrhea, nausea, vomiting).[40,64,132,136,139] Whereas BRAF/MEK inhibitor combination therapy was associated with higher risk of pyrexia and diarrhea, BRAF inhibitor monotherapy was associated with higher risk of musculoskeletal complaints. Alopecia, rash, and other skin toxicities are also common across all types of BRAF-targeted therapy, but in phase III trials most of these toxicities were actually more common with BRAF inhibitor monotherapy versus BRAF/MEK inhibitor combination therapy. Hyperproliferative skin toxicities had notably higher prevalence in patients treated with BRAF inhibitor monotherapies versus BRAF/MEK inhibitor combinations, including hyperkeratosis, palmoplantar disorders, keratoacanthoma, and cutaneous squamous cell carcinoma. Due to better efficacy and a different toxicity profile, specifically lower risk for certain proliferative skin toxicities, BRAF/MEK inhibitor combination therapy is generally preferred over BRAF inhibitor monotherapy. In clinical practice across NCCN member institutions, the change in prescribing patterns from using BRAF inhibitor monotherapy to using BRAF/MEK inhibitor combinations has resulted in lower rates of discontinuation due to hypoproliferative skin toxicities and musculoskeletal complaints; flu-like symptoms are still very common (with BRAF/MEK inhibitor combination) but seem less likely to lead to discontinuation of treatment, especially if patients are forewarned. There are rare patients who experience certain toxicities on BRAF/MEK inhibitor combination therapy that are thought to be attributed to MEK inhibitors (eg, deep venous thrombosis, retinal problems, concerns about immunosuppression), and in

Table 10. BRAF and MEK Inhibitors: Toxicities[a]

Studies	COMBI-d[b,64,136]				COMBI-v[40]				Co-BRIM[132]				COLUMBUS[139]					
Agent	Dab		Dab/Tram		Vem		Dab/Tram		Vem		Vem/Cobi		Vem		Encor		Encor/Bini	
Grade	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–4[c]	Any	3–4[c]	Any	3–4[c]	Any
All types	50	97	48	97	59	99	49	98	61	98	75	99	66	–	67	–	64	–
General, symptomatic:																		
Pyrexia	2	***	7	******	1	**	4	*****	0	**	1	***	0	***	1	*	4	**
Chills	1	**	1	***	0	*	1	***	0	*	0	*	–	–	–	–	–	–
Headache	1	***	1	***	1	**	1	***	2	**	<1	**	1	**	3	***	2	***
Fatigue	1	****	2	****	2	***	1	***	3	***	5	****	2	***	1	***	2	***
Asthenia	1[b]	*[b]	<1[b]	*[b]	1	**	1	**	1	**	2	**	4	**	3	**	2	**
Decreased appetite	1[b]	*[b]	<1[b]	*[b]	0	**	1	*	<1	**	0	**	1	**	1	**	0	*
Peripheral edema	1	*	1	**	<1	*	<1	*	<1	*	0	*	1	*	0	*	2	*
Cough	0	**	0	**	0	*	0	**	0	*	0	*	1	*	1	*	1	*
General, laboratory results:																		
Hypertension	6	**	6	**	10	**	14	***	3	*	6	**	3	*	3	*	6	*
ALT increased	1	*	2	*	4	**	3	*	6	**	11	***	2	*	1	*	5	*
AST increased	1		3	*	3	*	1	*	2	*	9	**	2	*	1		2	*
GGT increased	–	–	–	–	–	–	–	–	10	**	15	**	3	*	5	*	9	**
Blood CPK increased	–	–	–	–	–	–	–	–	<1		12	****	0		0		7	***
Blood ALP increased	–	–	–	–	–	–	–	–	2	*	5	**	1	*	0		1	*
Lipase increased	–	–	–	–	–	–	–	–	1		3		1		1		2	
Anemia	–	–	–	–	–	–	–	–	3	*	2	**	3	*	3	*	5	**
Musculoskeletal/Pain:																		
Arthralgia	0	***	1	***	4	*****	1	**	5	****	2	****	6	*****	9	****	1	***
Myalgia	0[b]	*[b]	<1[b]	*[b]	1	*	0	**	2	*	<1	**	1	**	10	***	0	**
Pain in extremity	–	–	–	–	<1	*	1	*	2	**	1	*	1	*	1	**	1	*
Pain	–	–	–	–	–	–	–	–	<1		0		0		4	*	1	
Musculoskeletal pain	–	–	–	–	–	–	–	–	<1	*	1		1	*	3	**	0	*

(continued on next page)

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

[a]AE rates shown are for all AEs, regardless of whether they were treatment related. Table includes all AEs that occurred in >20% of patients or as high grade (grade 3–4 of 3–5) in >3% of patients in any arm in any of the four trials shown. Values are percent of patients who experienced at least one AE of any grade, grade 3–4 or grade 3–5. For the any grade column, the percent of patients affected by specific AEs (any grade) was rounded to the nearest 10%, then assigned one asterisk (*) for every 10% of patients effected. Blank indicates that <5% of patients experienced the AE.

[b]For AEs not reported in Long et al 2017,[136] data from Long et al 2014[64] are shown. COMBI-d data are from Long et al 2017[136] unless otherwise noted.

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

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

Table 10. BRAF and MEK Inhibitors: Toxicities[a] (cont.)

Studies	COMBI-d[b,64,136]				COMBI-v[40]				Co-BRIM[132]				COLUMBUS[139]					
Agent	Dab		Dab/Tram		Vem		Dab/Tram		Vem		Vem/Cobi		Vem		Encor		Encor/Bini	
Grade	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–5	Any	3–4[c]	Any	3–4[c]	Any	3–4[c]	Any
Gastrointestinal:																		
Diarrhea	1	**	1	***	<1	****	1	***	1	***	7	******	2	***	2	*	3	****
Nausea	1	***	1	****	1	****	<1	***	1	***	1	****	2	***	4	****	2	****
Vomiting	1	*	1	***	1	**	1	***	1	*	2	***	1	**	5	***	2	***
Constipation	0[b]	*[b]	<1[b]	*[b]	<1	*	0	*	0	*	0	*	1	*	0	**	0	**
Cutaneous:																		
Rash	1	**	0	***	9	****	1	**	6	****	5	****	3	***	2	**	2	*
Pruritis	0[b]	*[b]	0[b]	*[b]	1	**	0	*	<1	**	1	**	0	*	1	**	1	*
Rash maculo-papular	–	–	–	–	–	–	–	–	5	**	7	**	4	*	1	*	0	
Rash generalized	–	–	–	–	–	–	–	–	1		<1		4	*	1	*	0	
Alopecia	0	***	1	*	<1	****	0	*	<1	***	<1	**	0	****	0	******	0	*
Dry skin	0[b]	*[b]	0[b]	*[b]	<1	**	0	*	0	**	1	**	0	**	0	***	0	**
Hyperkeratosis	1	****	0	*	1	**	0		2	***	<1	*	0	***	4	****	1	**
Keratosis pilaris	–	–	–	–	0	*	0		0	*	0		0	**	0	**	0	
Palmoplantar erythrodysesthesia syndrome	–	–	–	–	<1[d]	**[d]	0[d]	[d]	<1		0	*	1	*	14	*****	0	*
Palmoplantar keratoderma	1	**	1	*					0	*	0		1	**	2	***	0	*
Skin papilloma	0	**	0		1	**	0		<1	*	0	*	0	**	0	*	0	*
Photosensitivity reaction	0		0		<1	**	0		0	**	3	***	1	**	0		1	
Keratoacanthoma	1	*	2		–	–	–	–	9	*	1		3	*	0	*	1	
cSCC					<1		0		13	*	4		4	*	0		0	
Basal cell carcinoma	1	*	3		–	–	–	–	2		6	*	1		1		0	

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

[a]AE rates shown are for all AEs, regardless of whether they were treatment related. Table includes all AEs that occurred in >20% of patients or as high grade (grade 3–4 of 3–5) in >3% of patients in any arm in any of the four trials shown. Values are percent of patients who experienced at least one AE of any grade, grade 3–4 or grade 3–5. For the any grade column, the percent of patients affected by specific AEs (any grade) was rounded to the nearest 10%, then assigned one asterisk (*) for every 10% of patients effected. Blank indicates that <5% of patients experienced the AE.

[b]For AEs not reported in Long et al 2017,[136] data from Long et al 2014[64] are shown. COMBI-d data are from Long et al 2017[136] unless otherwise noted.

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

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

those cases discontinuation of the MEK inhibitor may be helpful. There are few data to inform selection among the BRAF/MEK inhibitor combination therapy options (dabrafenib/trametinib, vemurafenib/cobimetinib, encorafenib/binimetinib), as none of the options have been directly compared.

Grade 5 toxicities were rare (≤2% in phase III trials) in trials testing BRAF inhibitor monotherapy or BRAF/MEK inhibitor combination therapies.[40,128–132,136,139–141] Grade 5 AEs observed across trials included cardiovascular or cerebrovascular events (eg, brain/intracranial hemorrhage, brain ischemia, acute coronary syndrome, cardiac arrest/failure, acute myocardial infarction, pulmonary embolism), AEs related to infection (eg, pneumonia, pleural infection, sepsis), and multiorgan failure.[40,129,131,132,136,139] It is not clear which of these grade 5 AEs were really related to treatment. In addition to those shown in Table 10, reports from multiple clinical trials have highlighted a few other rare high-grade AEs of special interest, including an assortment of ocular AEs (eg, retinopathies, blurred vision, retinal detachment, uveitis), QT prolongation, decreased ejection fraction, thrombotic events, and the development of new primary malignancies.[37,40,65,67,136–138,141,147]

Analysis of data from the several prospective trials showed that for BRAF-targeted therapy, most AEs manifest within the first few months of therapy, although AEs continue to develop throughout treatment, albeit at a lower rate.[65,131,137,138] There is some evidence to suggest that time to onset may be longer for BRAF/MEK inhibitor combination therapy compared with BRAF inhibitor monotherapy, at least for some types of AEs.[137,138] In the COLUMBUS trial, median time to first occurrence of grade 3–4 toxicity was longer with encorafenib/binimetinib combination versus encorafenib or vemurafenib monotherapy (8.4 vs 2.8, 3.7 months).[138] In Co-BRIM, some of the most common AEs had early onset in both arms (pyrexia, rash, elevated creatine phosphokinase, liver function test abnormality), whereas diarrhea was quick to develop in the cobimetinib/vemurafenib combination therapy arm, but took longer to develop in the vemurafenib monotherapy arm.[137] Regardless of treatment, cutaneous squamous cell carcinoma/keratoacanthoma, photosensitivity, serous retinopathy, and left ventricular ejection fraction decline tended to have wider ranges of time to onset (and therefore longer median time to onset) than other types of AEs.[137] Results from a large stage IV trial testing vemurafenib also reported that time to onset for cutaneous squamous cell carcinoma was longer than for other types of AEs.[65] Results from the Co-BRIM trial suggest that for these cutaneous AEs and ocular AEs, median time to onset was longer with cobimetinib/vemurafenib versus vemurafenib monotherapy.[137] Time to resolution varied across different type of AEs and type of treatment, although the majority resolved within 3 months.[137]

Other Options for Unresectable or Distant Metastatic Disease

For discussion of data on the efficacy of other systemic therapy options (imatinib, interleukin-2, cytotoxic therapy) for the treatment of metastatic melanoma, and radiation therapy for extracranial metastases, see full NCCN Guidelines for Cutaneous Melanoma, available at NCCN.org.

Treatment of Brain Metastases

For discussion of data informing treatment of brain metastases, including surgery, radiation, and combining systemic therapy with radiation, see full NCCN Guidelines for Cutaneous Melanoma, available at NCCN.org.

NCCN Recommendations for Distant Metastatic Disease

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

Recommendations for Limited Metastatic Disease

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

If completely resected, patients with no evidence of disease (NED) can be observed or offered adjuvant treatment. The choice of adjuvant systemic treatment versus observation should take into consideration the patient's risk of melanoma recurrence and the risk of treatment toxicity. The recommended adjuvant treatment options are described in the section, "Adjuvant Systemic Therapy for Melanoma" (page 368).

Patients with residual disease after incomplete resection for limited metastases should be treated as described in the next section for disseminated disease.

Recommendations for Disseminated Disease

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

A number of options are available for systemic therapy, as described in the next sections.

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

For brain metastases, recommended localized treatment options and considerations for selecting systemic therapy are described in the section, "Treatment of Patients with Brain Metastases" (available in the discussion section of these guidelines at NCCN.org).

For patients considering multimodality therapy for disseminated disease, interactions between radiation therapy and systemic therapies (eg, BRAF inhibitors, IFN alfa-2b, immune checkpoint inhibitors) need to be very carefully considered, as there is potential for increased toxicity, particularly when using higher doses of radiation. Because BRAF and/or MEK inhibitors may interact with radiation, consideration should be given to holding BRAF and/or MEK inhibitors ≥3 days before and after fractionated RT and ≥1 day before and after stereotactic radiosurgery (or other high-dose-per-fraction regimens).[148]

Except for patients rendered NED by surgery, all patients undergoing active treatment of distant metastatic disease should be regularly assessed for response or progression, both by clinical exam and imaging. Recommended imaging modalities are the same as for initial workup, as described in the section "General Guidelines for Imaging in Patients with Melanoma" (available online, in the discussion section of these guidelines, at NCCN.org).

Recommendations for Systemic Therapy

Recommendations for First-line Systemic Therapy

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

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

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

Selection between anti-PD-1 monotherapy and nivolumab/ipilimumab combination therapy should be informed by the consideration that, although combination therapy may improve PFS relative to nivolumab monotherapy, it is associated with a much higher risk of serious immune-mediated toxicities compared with nivolumab monotherapy. Treatment selection should therefore be informed by consideration of the patient's overall health, medical history, concomitant therapies, comorbidities, and compliance with proactive monitoring and management of AEs. Relative indications for combination nivolumab/ipilimumab in comparison with PD-1 monotherapy include: patient willingness to take on high risk of irAEs; absence of comorbidities or autoimmune processes that would elevate the risk of irAEs; patient social support and anticipated compliance with medical team to handle toxicities; and absent/low tissue PD-L1 expression.

For patients with unresectable or distant metastatic disease harboring a *BRAF* V600-activating mutation, BRAF-targeted therapy first-line options include BRAF/MEK inhibitor combination therapy with dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib. All of these regimens are category 1 options based on results from phase 3 trials in the first-line setting (ie, COMBI-d, COMBI-v, CoBRIM, and COLUMBUS). Although vemurafenib and dabrafenib are FDA approved as single-agent therapy for treatment of patients with distant metastatic or unresectable melanoma with *BRAF* V600E

mutation,[149,150] these agents are almost never given without concomitant MEK inhibition. BRAF/MEK inhibitor combination therapy has been shown to have superior response rate, PFS, and OS compared with BRAF inhibitor monotherapy, as well as a similar or better toxicity profile, so the NCCN panel recommends BRAF inhibitor monotherapy only in those rare cases where combination therapy is contraindicated. In such cases, BRAF inhibitor monotherapy remains a treatment option, especially if the patient is not an appropriate candidate for immune checkpoint inhibitor therapy. Dabrafenib/trametinib, vemurafenib/cobimetinib, and encorafenib/binimetinib combination therapy regimens are FDA approved for the treatment of patients with unresectable or distant metastatic melanoma with *BRAF* V600E or V600K mutations, as detected by an approved test.[149–154] The Cobas 4800 *BRAF* V600 mutation test, a test for detecting the *BRAF* V600E mutation, received FDA approval as a companion diagnostic for selecting patients for treatment with vemurafenib. The THxID BRAF Kit, a test for detecting *BRAF* V600E or V600K mutations, received FDA approval as a companion diagnostic for selection of patients for treatment with dabrafenib and trametinib. The NCCN panel recommends that *BRAF* mutational status should be tested using an FDA-approved test or by a facility approved by the Clinical Laboratory Improvement Amendments (CLIA). Positive immunohistochemistry (IHC) staining of tumor for VE1 is sufficient for starting targeted therapy in patients who are symptomatic or have rapidly progressing disease. Due to risk of false positives and false negatives, all VE1 IHC results, both positive and negative, should be confirmed by sequencing. The NCCN panel recommends that tissue for genetic analysis be obtained from either biopsy of a current metastasis (preferred) or from archival material. The NCCN panel considers BRAF/MEK inhibitor combination therapy (or single-agent BRAF inhibitor therapy if combination therapy is contraindicated) as appropriate treatment options for metastatic disease with any type of activating *BRAF* V600 mutation (includes V600E, V600K, V600R, V600D, and others). Although trametinib is FDA approved for single-agent use to treat patients with unresectable or metastatic melanoma with *BRAF* V600E mutation,[153] trametinib monotherapy is no longer an NCCN-recommended treatment option due to relatively poor efficacy compared with BRAF inhibitor monotherapy and BRAF/MEK inhibitor combination therapy.

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

When to Discontinue Treatment or Switch Systemic Therapy

Consistent with the FDA prescribing information, the NCCN panel recommends discontinuing systemic therapy in cases of unacceptable toxicity. If there is residual disease at the time of discontinuation, it is recommended to switch to a different class of therapy. See section, "Guidelines for Therapy Selection in Previously Treated Patients" (page 396).

All patients undergoing systemic therapy for distant metastatic disease should be regularly assessed for response or progression, both by clinical exam and imaging. Recommended imaging modalities are the same as for initial workup, as described in the section entitled "General Guidelines for Imaging in Patients with Melanoma" (available online, in the discussion section of these guidelines, at NCCN.org).

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

disease progression. The optimal duration to administer BRAF-targeted therapy after achieving a durable CR, PR, or SD is not known.

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

Recommendations for Second-Line or Subsequent Therapy

For patients with previously treated distant metastatic disease, data on the efficacy and safety of specific systemic therapies are in general less robust than data in the first line setting. For a wide variety of agents there are prospective data demonstrating activity in previously treated patients, but prospective trials comparing these options are limited, and largely included patients whose previous therapies did not include the BRAF-targeted and immune checkpoint inhibitor options that are now preferred for first-line therapy. Interpretation of data from this setting is challenging because the patient population is highly heterogenous in terms of the number and types of previous systemic therapies received, location and extent of metastatic disease, and speed of progression (symptomatic or not). Given the lack of high quality data and the wide array of scenarios that present in the clinic, the NCCN panel lists a large number of acceptable options for second-line or subsequent systemic therapy, with the general recommendation to consider therapies whose mechanism of action differs from prior lines of therapy that resulted in poor response or disease progression. The subsequent sections first describe the rationale for including each of the options listed for second-line or subsequent systemic therapy, and then discuss recommendations for selecting among these options.

Options for Second-Line or Subsequent Systemic Therapy: BRAF-Targeted Therapies and Immune Checkpoint Inhibitors

Based on the positive results from phase III trials supporting the recommended first-line therapies, the following immune checkpoint inhibitors and BRAF-targeted therapy regimens have been incorporated into the guidelines as options for second-line or subsequent systemic therapy for qualifying patients: nivolumab, pembrolizumab, nivolumab/ipilimumab combination, dabrafenib/trametinib, vemurafenib/cobimetinib, or encorafenib/binimetinib combination. Due to lack of phase III trial data in patients with previously treated metastatic disease, however, these regimens are category 2A (rather than category 1) recommended options for second-line or subsequent systemic therapy. As described in previous sections, results from phase I/II trials in patients with previously-treated advanced disease support second-line or subsequent systemic therapy for some of these options (eg, vemurafenib/cobimetinib, dabrafenib/trametinib, pembrolizumab). Use of nivolumab monotherapy in previously treated patients is supported by phase III trial data in this setting (Checkmate 037), although the results were less robust than those seen in the first-line setting. As in the first-line setting, BRAF inhibitor monotherapy is only recommended in the context of contraindications to BRAF/MEK inhibitor combination therapy, BRAF-targeted therapy (BRAF inhibitor monotherapy or BRAF/MEK inhibitor combination therapy) is only recommended for patients with *BRAF* V600 activating mutations, and there is no panel consensus on use of PD-L1 expression as a biomarker for selection of anti-PD-1 therapy (monotherapy or nivolumab/ipilimumab combination). See section on "Recommendations for First-line Systemic Therapy" (page 393) for guidance on *BRAF* mutation testing.

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

Options for Second-line or Subsequent Systemic Therapy: Interleukin-2

Although associated with significant risk of severe toxicity, interleukin-2 remains an option in the second-line or subsequent setting because it can provide long-term survival for the small percent of patients (<10%) with CR.[155–159] Due to the low response rate and high toxicity, however, interleukin-2 is not a preferred option as it is considered less safe and less effective than immune checkpoint inhibitors or BRAF-targeted therapy options.

Options for Second-line or Subsequent Systemic Therapy: T-VEC ± Ipilimumab

Based on the results from a randomized phase II trial showing that intralesional T-VEC improved response rate in patients treated with systemic ipilimumab,[160] this combination is listed as an option for patients with injectable metastases. Because results of the trial did not demonstrate improved PFS or OS, ipilimumab/T-VEC combination therapy is a category 2B recommendation, only listed as an option for second or subsequent-line therapy (not first-line therapy) and is not a preferred option. Although anti-PD-1 therapy is generally preferred over ipilimumab, the NCCN panel voted not to include combination therapy with T-VEC plus systemic anti-PD-1 therapy as a recommended option, both because there are insufficient randomized trial data on this specific combination, and because the effect of adding T-VEC to ipilimumab was fairly modest.

Options for Second-line or Subsequent Systemic Therapy: Imatinib

Activating *KIT* mutations are rare in patients with cutaneous melanoma, but for those who have them, imatinib may be helpful for disease control. Among patients with activating *KIT* mutations, fewer than half responded to imatinib, and randomized trials to assess impact on PFS and OS have not been conducted.[161–163] For these reasons imatinib is not listed as a preferred agent, even for patients with qualifying mutations, but may be useful for those who are ineligible for or unresponsive to more effective therapies (ie, immune checkpoint inhibitors, BRAF-targeted therapy).

Options for Second-line or Subsequent Systemic Therapy: Cytotoxic Therapy

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

Options for Second-line or Subsequent Systemic Therapy: Best Supportive Care

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

Guidelines for Therapy Selection in Previously Treated Patients

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

In general, if a patient experienced progression of melanoma during or shortly after a systemic therapy, rechallenge with the same therapy or therapy of the same class is unlikely to yield a response and is not recommended. The exception to this rule is that for patients who progressed on single-agent immune checkpoint inhibitor therapy, nivolumab/ipilimumab combination therapy is a reasonable treatment option. In addition, although anti-CTLA-4 (ipilimumab) and anti-PD-1 (nivolumab, pembrolizumab) agents are both immune checkpoint inhibitors, they are not considered the same class of agent because they target different molecules. Therefore, for patients who previously received ipilimumab, subsequent treatment with anti-PD-1 therapy is a recommended option, and vice versa. Given that for both immune checkpoint inhibitors and BRAF-targeted therapy there are data showing responses upon rechallenge, the NCCN panel recommends that, for patients who experience disease control (CR, PR, or SD) and have no residual toxicity, but

subsequently experience disease progression/relapse >3 months after treatment discontinuation, reinduction with the same agent or same class of agents may be considered.

Immune Checkpoint Inhibitor Administration

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

Treatment-related AEs occur in a high percentage of patients treated with anti-CTLA-4 or anti-PD-1 agents, and grade 3–4 related AEs occur in as many as 22% of patients receiving anti-PD-1 therapy, 20%–30% of patients receiving ipilimumab monotherapy, and in 50%–60% of patients receiving nivolumab/ipilimumab combination therapy. Careful selection of patients and AE monitoring and management are therefore critical to safe administration of all of these agents. Among other factors, patient selection should take into consideration age, comorbidities (eg, disease processes whose manifestations might be confused with immune-related toxicities), concomitant medications (eg, immunosuppressive therapies), and overall performance status. Patients with underlying autoimmune disorders are generally excluded from treatment with immune checkpoint inhibitors.

Close monitoring of potentially lethal irAEs in patients receiving immune checkpoint inhibitors is essential. In addition to proactive questioning of symptoms, patient and nursing education and frequent communication with the care team are essential for identifying and effectively managing irAEs. Recommendations for monitoring and management immune-related toxicities associated with immune checkpoint inhibitors are summarized in the NCCN Guidelines for Management of Immunotherapy-Related Toxicities (available at NCCN.org). There are 2 broad categories of irAE monitoring and management: one for ipilimumab-containing regimens and one for anti-PD-1 monotherapy. Clinicians need to educate themselves about the pattern of toxicities and recognition of these toxicities, as well as management strategies. Formal training programs are strongly recommended, along with careful and frequent consultation of (1) the NCCN Guidelines for Management of Immunotherapy-Related Toxicities[164] and the relevant package inserts[45,53,116]; (2) other FDA-approved materials with detailed descriptions of the signs and symptoms of irAEs associated with ipilimumab and detailed protocols for management[165]; and (3) standard institutional protocols for monitoring and managing irAEs, with multidisciplinary input among various specialists as warranted.

Prevention and Management of BRAF Inhibitor Toxicities

Fever is common in patients receiving BRAF-targeted therapy and is often episodic, with onset often 2–4 weeks following the start of therapy. Pyrexia may be associated with chills, night sweats, rash, dehydration, electrolyte abnormalities, and hypotension. Pyrexia should be managed by treatment discontinuation and use of antipyretics such as acetaminophen and/or NSAIDs. Stopping or holding BRAF/MEK inhibitor therapy at the onset of pyrexia will often interrupt the episode. After resolution of fever and pyrexia related symptoms, resumption of BRAF/MEK inhibitor treatment at reduced dose may be tried. Upon re-exposure, repeat pyrexia events can occur. Patients treated with BRAF-targeted therapy should also be educated to report joint pain and swelling, visual changes, and cutaneous manifestations. Patients who develop skin complications should be promptly referred to a dermatologist for management and monitoring. Patients should be advised about the possibility of photosensitivity associated with these agents, and counseled to minimize ultraviolet exposure and use ultraviolet-protective clothing and high-SPF sunblock.

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

Management of Interleukin-2 Toxicities

For recommendations for management of toxicities associated with interleukin-2, see full NCCN Guidelines for Cutaneous Melanoma, available at NCCN.org.

Recommendations for Treatment of Patients With Brain Metastases

For recommendations for treatment of brain metastases, including surgery, radiation, and/or systemic therapy, see full NCCN Guidelines for Cutaneous Melanoma, available at NCCN.org.

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The NCCN Guidelines Staff have no conflicts to disclose.