NCCN Guidelines® Insights
Featured Updates to the NCCN Guidelines

Abstract
The NCCN Guidelines for Melanoma have been significantly revised over the past few years in response to emerging data on a number of novel agents and treatment regimens. These NCCN Guidelines Insights summarize the data and rationale supporting extensive changes to the recommendations for systemic therapy in patients with metastatic or unresectable melanoma.

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The therapeutic landscape for metastatic melanoma is rapidly changing with the recent development of novel agents, which have demonstrated better efficacy than traditional chemotherapy. The first generation of novel targeted and immunotherapy agents (ie, vemurafenib, dabrafenib, and ipilimumab) demonstrated significantly improved response rates and outcomes compared with conventional therapies. Subsequently, a number of ongoing or recently completed phase II and III trials testing new immunotherapies, targeted therapies, and combination regimens have yielded noteworthy results. A second generation of effective agents and combination regimens is now available for the treatment of advanced unresectable or metastatic melanoma. These NCCN Guidelines Insights focus on the efficacy data supporting revisions to the recommendations for treatment of unresectable or metastatic melanoma; safety data and guidelines for adverse event management are summarized in the full discussion.

### NCCN Categories of Evidence and Consensus

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

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

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

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

**All recommendations are category 2A unless otherwise noted.**

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

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<table>
<thead>
<tr>
<th>FIRST-LINE THERAPY</th>
<th>SYSTEMIC THERAPY FOR METASTATIC OR UNRESECTABLE DISEASE</th>
<th>PERFORMANCE STATUS (PS)</th>
<th>SECOND-LINE OR SUBSEQUENT THERAPY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic or unresectable disease</td>
<td>Immunotherapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>Pembrolizumab (category 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti PD-1 monotherapy</td>
<td>Nivolumab (category 1)</td>
<td></td>
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<tr>
<td>Ipilimumab (category 1)</td>
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<td></td>
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<tr>
<td>Targeted therapy if BRAF mutated; preferred if clinically needed for early response</td>
<td>Dabrafenib/trametinib (category 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combination therapy (preferred)</td>
<td>Vemurafenib/cobimetinib (category 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-agent therapy</td>
<td>Vemurafenib (category 1)</td>
<td></td>
<td></td>
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<tr>
<td>Dabrafenib (category 1)</td>
<td>Clinical trial</td>
<td></td>
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</tbody>
</table>

**Systemic Therapy**

**First-Line Therapy**

- Pembrolizumab
- Nivolumab
- Ipilimumab
- Dabrafenib/trametinib
- Vemurafenib/cobimetinib
- Vemurafenib
- Dabrafenib

**Second-Line or Subsequent Therapy**

- Pembrolizumab
- Nivolumab
- Ipilimumab
- Vemurafenib/cobimetinib
- Dabrafenib/trametinib
- Vemurafenib
- Dabrafenib
- High-dose IL-2
- Biochemotherapy
- Imatinib for tumors with activating mutations of C-KIT
- Clinical trial

**Performance Status (PS)**

- PS 0–2: Disease progression or Maximum clinical benefit from BRAF targeted therapy
- PS 3–4: Consider best supportive care (See NCCN Guidelines for Palliative Care)
text of the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Melanoma (to view the most recent version of these guidelines, visit NCCN.org). Depending on the circumstances, systemic therapy may not be the only recommended option for treatment of metastatic disease. See the full NCCN Guidelines for Melanoma for the complete recommendations for treatment of metastatic melanoma, including non-systemic treatment modalities and treatment of brain metastases.

Systemic Therapy for Advanced Melanoma

Checkpoint Immunotherapy

Some of the most effective immunotherapies target immune checkpoints exploited by cancers to decrease immune activity. For example, activation of T-helper cells upon binding to antigens on the antigen-presenting cell (APC) can be modulated by other receptor-ligand interactions between the 2 cells. Cytotoxic T-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (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. Antibodies against these receptors (ipilimumab, nivolumab, pembrolizumab) prevent receptor-ligand interaction, removing the inhibition of T-cell activation and “releasing the brake” on the immune response.

Pembrolizumab: Randomized trials in patients with unresectable stage III or IV metastatic disease have shown that pembrolizumab (monotherapy), like nivolumab, improves response and progression-free survival (PFS) compared with chemotherapy or ipilimumab (monotherapy), and is associated with lower risk of adverse events (Table 1). Results from KEYNOTE-006 showed that pembrolizumab also improved overall survival (OS) compared with ipilimumab. The efficacy and safety of pembrolizumab did not appear to be significantly affected by the dose level (2 mg/kg vs 10 mg/kg) and frequency (every 2 weeks [Q2W] or every 3 weeks [Q3W]), and all the regimens tested in these trials improved response and outcomes compared with controls.

Nivolumab: Two phase III clinical trials have demonstrated nivolumab efficacy in previously untreated unresectable stage III or IV melanoma (Table 2). Results from CheckMate 066 showed that nivolumab improved response rate, PFS, and OS compared with chemotherapy. The percent grade 3/4 adverse events was lower with nivolumab compared with chemotherapy. Remarkably, the survival curve suggests that nivolumab may lead to long-term survival in at least 50% of patients. Results from CheckMate 067 showed that nivolumab (monotherapy) improved response rate and PFS compared with single-agent ipilimumab, and was associated with lower toxicity.

The results of CheckMate 066 and 067 demonstrated that, in the first-line setting, nivolumab is a better option than chemotherapy or ipilimumab for patients with unresectable or metastatic disease. An ongoing trial, CheckMate 037, has shown that nivolumab also improves response rate compared with chemotherapy in patients with previously treated unresectable stage III or IV melanoma (Table 2). Safety results suggest that nivolumab may be better tolerated than chemotherapy in heavily pretreated patients with advanced disease. Further follow-up is needed to verify whether nivolumab improves PFS or OS in patients with previously treated advanced disease.

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

As shown in Table 2, results from 2 randomized trials demonstrated that ipilimumab/nivolumab combination therapy significantly improved response and PFS compared with ipilimumab monotherapy in patients with previously untreated unresectable stage III or IV disease. Further follow-up is needed to determine whether nivolumab/ipilimumab combination therapy improves OS compared with single-agent ipilimumab. Both these trials also showed substantially increased toxicity with immune checkpoint combination therapy versus monotherapy.

Anti-PD-1 Therapy in Patient Subpopulations:

BRAF Mutation Status: Subgroup analyses in the CheckMate and KEYNOTE trials showed that both patients with BRAF-mutant tumors and those with BRAF wild-type tumors derived clinical benefit from anti-PD-1 therapy compared with controls (single-agent ipilimumab or chemotherapy). 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.
**Melanoma, Version 3.2016**

### Table 1. Pembrolizumab Trials in Advanced Melanoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase, Design</th>
<th>Patients</th>
<th>Treatment Arms</th>
<th>Responsea</th>
<th>Grade 3/4 AEs</th>
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<tbody>
<tr>
<td>KEYNOTE-001 NCT0129582723</td>
<td>I R, OL, E</td>
<td>Nonea</td>
<td>Pembro 2 mg/kg (n=89)</td>
<td>26% 2.8 ND 5.1</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pembro 10 mg/kg (n=84)</td>
<td>26% 2.8 ND 3.2</td>
<td>63% 8%</td>
</tr>
<tr>
<td>KEYNOTE-002 NCT01704287</td>
<td>II R, OL</td>
<td>Nonea</td>
<td>Pembro 2 mg/kg (n=180)</td>
<td>21% P&lt;.0001 3 ND 2.9 P&lt;.0001 ND</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pembro 10 mg/kg (n=181)</td>
<td>25% P&lt;.0001 3.5 ND 2.9 P&lt;.0001 ND</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemoa (n=179)</td>
<td>4% 3 37 2.7 ND</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>KEYNOTE-006 NCT0186631922</td>
<td>III R, OL</td>
<td>34%</td>
<td>Pembro Q2W (n=279)</td>
<td>34% P&lt;.001 2.8 8.3 5.5 P&lt;.001 74% P&lt;.0005</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pembro Q3W (n=277)</td>
<td>33% P&lt;.001 2.8 ND 4.1 P&lt;.001 68% P&lt;.0036</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ipi (n=278)</td>
<td>12% 2.9 ND 2.8</td>
<td>58% 20%</td>
</tr>
</tbody>
</table>

Abbreviations: **BRAF** V600 Mut, percentage of patients with a mutation in **BRAF** at V600; Chemo, chemotherapy; **Brain Mets**, percentage of patients with brain metastases at baseline; E, expansion; ipi, ipilimumab; ND, not determined because longer follow-up is needed; NR, not reported; OL, open label; OS, overall survival; pembro, pembrolizumab; **PFS**, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomized; Tx, treatment.

*Unresectable stage III or IV melanoma.*

*Previously untreated advanced disease.*

*Patients with active brain metastases were excluded from the trials.*

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

*Median PFS is given in months. OS is given as 1-year rate. Median duration and *P* value were determined using the Kaplan-Meier method. *P* values are for comparisons with the control arm.*

*Percentage of patients who experienced any type of treatment-related AE of grade 3 or 4.*

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

*Investigator’s choice chemotherapy.*

*Median PFS varied by method of assessment; for all analyses *P*<.0001.

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**PD-L1 Expression:** To determine whether the PD-1 ligand (PD-L1) could be used to identify candidates for anti–PD-1 therapy, PD-L1 expression was assessed in tumor samples from patients in the CheckMate and KEYNOTE trials, and expression level cutoffs were chosen to divide patients into “PD-L1–positive” and “PD-L1–negative” subgroups.14,21 Across trials, results showed that for both subgroups, anti–PD-1 monotherapy provided clinical benefit compared with controls (single-agent ipilimumab or chemotherapy), and nivolumab/ipilimumab combination therapy improved efficacy compared with ipilimumab. The apparent prognostic value of PD-L1 may have been limited by the expression assays and cutoffs used in these studies. Although PD-L1 expression assays continue to be developed, they are not in current form sufficiently reproducible, widely available, nor discriminative for screening patients with melanoma.

**Brain Metastases:** In the CheckMate and KEYNOTE trials, 3% to 19% of patients had brain metastases (Tables 1 and 2). Ongoing trials have been designed to specifically address the safety and efficacy of anti–PD-1 in patients with melanoma brain metastases (ClinicalTrials.gov identifiers: NCT02320058, NCT02374242, and NCT02621515).

**Before or After Anti–CTLA-4 Therapy:** Ongoing studies are aimed at determining the efficacy of sequential monotherapy with ipilimumab and PD-1 inhibitor. Preliminary results from a randomized phase II trial show similar safety but improved response for patients treated with nivolumab followed by ipilimumab compared with patients who received these therapies in the reverse order.24

**Checkpoint Immunotherapy Treatment Administration:** The ipilimumab treatment regimen of 3 mg/kg Q3W for 4 doses is well supported by clinical trial data and approved by the FDA.25–27 For anti–PD-1 agents, however, there are fewer data to support the optimal dose and duration of treatment. Tables 3 through 5 summarize the treatment dosing and dura-
Although the product labels for nivolumab and pembrolizumab indicate that treatment should continue until disease progression or unacceptable toxicity, the published trials allowed shorter or longer treatment in certain situations. Discontinuation is common among patients treated with anti–PD-1 therapy, and hence clinical experience with treatment beyond 1 year is currently limited. For the trials listed in the tables, results published thus far (median follow-up <2 years) show discontinuation rates of 45% to 77% in patients treated with anti–PD-1 therapy. In the KEYNOTE-002 study, pembrolizumab was administered for a maximum of 24 months. Further follow-up should indicate whether anti–PD-1 treatment beyond 2 years is needed to maintain disease control. Studies are needed to explore this question and test whether switching to lower-frequency maintenance therapy is sufficient to maintain long-term clinical benefit.

**BRAF-Targeted Therapies**

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

**BRAF Inhibitor Monotherapy:** Vemurafenib and dabrafenib were developed to inhibit BRAF with mutations at V600. For patients with previously untreated stage IV or unresectable stage III melanoma, phase III trials (BRIM-3, BREAK-3) have shown that monotherapy with either of these agents improves response rates, PFS, and OS compared with chemotherapy (dacarbazine; Tables 6–8). For both vemurafenib (Table 6) and dabrafenib (Table 7), efficacy in patients with previously treated advanced disease, including those who received prior ipilimumab, is supported by single-arm open-label trials (ClinicalTrials.gov identifier: NCT00949702; BREAK-2) showing response rates, median PFS, and median OS similar to those from the phase III trials (BRIM-3, BREAK-3). Phase III trial results show that time to response for BRAF inhibitors (median \( \approx 1.5 \) months) was shorter than with chemotherapy (Table 7), and when compared with data from other trials, seems to be shorter than for checkpoint immunotherapy (median, 2.1–3.5 months; Tables 1, 2, 6–8). Responses to BRAF inhibitor monotherapy were relatively short-lived, however, with median duration of approximately 5 to 7 months (Tables 6 and 7). Likewise, PFS and OS Kaplan-Meier curves for vemurafenib and dabrafenib show little or no decline during the first few months of treatment (\( \approx 1.5 \) months for PFS, \( \approx 3 \) months for OS), and then abruptly begin to decline. Both dabrafenib and vemurafenib have been tested in noncomparative trials (ClinicalTrials.gov identifier: NCT01307397; BREAK-MB) as single-agent therapy in patients with asymptomatic brain metastases (Table 6 and 7). Response rates for vemurafenib (24%) and dabrafenib (31%–38%; Table 7) were lower than for patients without brain metastases, but are nonetheless notable in the context of this difficult-to-treat population.

**BRAF/MEK Inhibitor Combination Therapy:** Despite high initial response rates, half of the patients treated with BRAF-targeted monotherapies relapse within around 6 months, due to development of drug resistance. Alternate methods for targeting the MAP kinase pathway are being explored as options for overcoming resistance to BRAF inhibitor therapy. Trametinib and cobimetinib are oral small-molecule inhibitors of MEK1 and MEK2, signaling molecules...
downstream of BRAF in the MAP kinase pathway. Results from a phase III randomized trial (ClinicalTrials.gov identifier: NCT01245062) showed that in patients with BRAF-mutated metastatic melanoma not previously treated with BRAF inhibitors, trametinib improved PFS and OS compared with chemotherapy.39 Although the response rate for trametinib (22%) was significantly better than for chemotherapy (8%; P=.01), it was lower than that for vemurafenib (48%, 53%) and dabrafenib (50%) from phase II and III trials.12,33,34 Moreover, in an open-label phase II study, trametinib failed to induce objective responses in 40 patients previously treated with a BRAF inhibitor.41

Although MEK inhibitor monotherapy has limited utility for treating advanced metastatic melanoma, phase III trials have now demonstrated that combination therapy with a BRAF and MEK inhibitor has better efficacy than BRAF inhibitor monotherapy for previously untreated unresectable or metastatic disease (Table 8).12,20,41 When compared with either single-agent dabrafenib or single-agent vemurafenib, combination therapy with dabrafenib and trametinib improved response rate, duration of response, PFS, and OS.12,20 Likewise, combination therapy with vemurafenib and cobimetinib improved response and PFS compared with single-agent vemurafenib.41 Further follow-up is needed to determine whether vemurafenib/cobimetinib also improves OS.

Little clinical data are available regarding the efficacy of BRAF/MEK combination therapy in patients with previously treated advanced melanoma. Results from phase I/II studies (Table 8) showed that in patients whose disease had progressed on previous BRAF inhibitor treatment, dabrafenib/trametinib combination therapy was associated with a relatively

### Table 5. Ipilimumab/Nivolumab Combination Treatment Regimens

<table>
<thead>
<tr>
<th>Trial</th>
<th>Dosing</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>CheckMate 067</td>
<td>1 mg/kg nivo + 3 mg/kg ipi (same day), Q3W for 4 doses; then 3 mg/kg nivo monotherapy Q2W</td>
<td>Until disease progression or unacceptable toxicity. Patients who had clinical benefit could opt for treatment beyond progression, provided they had not experienced substantial AEs.</td>
</tr>
<tr>
<td>CheckMate 069</td>
<td>1 mg/kg nivo + 3 mg/kg ipi (same day)</td>
<td>Until disease progression or unacceptable toxicity. Patients who had clinical benefit could opt for treatment beyond progression, provided they had not experienced substantial AEs.</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; ipi, ipilimumab; nivo, nivolumab; Q2W, once every 2 weeks; Q3W, once every 3 weeks.

### Table 6. Vemurafenib Monotherapy in Advanced Melanoma: Key Trials

<table>
<thead>
<tr>
<th>Name/ ClinicalTrials.gov Identifier</th>
<th>Phase, Design</th>
<th>Tx-Naivea</th>
<th>Brain Metsa</th>
<th>BRAF V600E (K)b</th>
<th>Treatment Arms</th>
<th>Responsec</th>
<th>AEs by Graded</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIM-3 NCT010069801,40</td>
<td>III R, OL</td>
<td>100%</td>
<td>91% (9%)</td>
<td>NRRA</td>
<td>Vem (n=337) DTIC (n=338)</td>
<td>48% 1.5 P=.001 NR 6.9 P&lt;.0001 OS 13.6 P&lt;.0008 65% 6% 2%</td>
<td></td>
</tr>
<tr>
<td>NCT01307397c</td>
<td>IV OL</td>
<td>50%</td>
<td>Allb 23%c</td>
<td>Vem (n=3,222) 34% NR 7.3 5.6 12.0 45% 3% 3%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT00949702a,14 15</td>
<td>II OL</td>
<td>None</td>
<td>92% (8%)</td>
<td>Vem (n=132) 53% NR 6.7 6.8 15.9 60% 4% &lt;1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; BRAF V600E, percentage of patients with the V600E BRAF mutation; Brain mets, percentage of patients with brain metastases at baseline; DTIC, dacarbazine; NR, not reported; OL, open label; OS, overall survival; PFS, progression-free survival; R, randomized; Tx, treatment; vem, vemurafenib.

1Unresectable stage III or IV melanoma; NCT00949702 included only stage IV melanoma.
2Previously untreated advanced disease.
3Response rate is the percentage of patients that achieved complete or partial response. Time to response is given in months. Response duration is given as the median, in months, unless otherwise indicated. P values are for comparisons with the control arm.
4Median PFS is given in months. OS is given as 1-year rate. Median duration and P value were determined using the Kaplan-Meier method. P values are for comparisons with the control arm.
5Percent of patients with AE of any cause (treatment or otherwise). None of these trials reported rates for treatment-related AEs.
6Data in parentheses indicate the percentage of patients with BRAF V600K mutation.
7Patients with active brain metastases were excluded from the trials.
8All treated patients had a BRAF V600 mutation.
9Response rate was 24% for patients with brain mets.

### NCCN Recommendations

**First-Line Systemic Therapy**

For first-line therapy of unresectable or metastatic disease, recommended treatment options include checkpoint immunotherapy, BRAF-targeted therapy for patients with BRAF-mutated disease, or clinical trial (see ME-E, page 947).

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

Although ipilimumab is FDA-approved for the 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 results from the CheckMate 067 phase III trial showing improved outcomes with anti–PD-1 monotherapy or nivolumab/ipilimumab combination therapy compared with ipilimumab monotherapy.

Selection between anti–PD-1 monotherapy and nivolumab/ipilimumab combination therapy should be informed by the consideration that although combination therapy has been shown to provide somewhat better PFS, it is associated with a much higher risk of serious immune-mediated toxicities, and there is currently no evidence of improvement in OS. 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 adverse events.

For patients with BRAF-mutant metastatic disease, BRAF-targeted first-line therapy options include BRAF/MEK inhibitor combination therapy.

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Table 7. Dabrafenib Monotherapy in Advanced Melanoma: Key Trials

<table>
<thead>
<tr>
<th>Name/ ClinicalTrials.gov Identifier</th>
<th>Phase, Design</th>
<th>BRAF V600E (K)</th>
<th>Brain Mets</th>
<th>TX-Naive&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Treatment Arms</th>
<th>Response&lt;sup&gt;+&lt;/sup&gt;</th>
<th>Grade 3/4 AEs&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>BREAK-2 NCT01153763&lt;sup&gt;10,11&lt;/sup&gt;</td>
<td>II, OL</td>
<td>16%</td>
<td>83% (17%)</td>
<td>0%</td>
<td>Dab (n=92)</td>
<td>59% (13%)</td>
<td>1.3</td>
</tr>
<tr>
<td>BREAK-3 NCT01227889&lt;sup&gt;12,13&lt;/sup&gt;</td>
<td>III, R, OL</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
<td>Dab (n=187)</td>
<td>50%</td>
<td>1.5</td>
</tr>
<tr>
<td>BREAK-MB NCT01266967&lt;sup&gt;14&lt;/sup&gt;</td>
<td>II, OL</td>
<td>52%</td>
<td>81% (19%)</td>
<td>100%&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Dab (n=172)</td>
<td>31%–38% (0%–28%)</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; BRAF V600E, percentage of patients with the V600E BRAF mutation; Brain mets, percentage of patients with brain metastases at baseline; dab, dabrafenib; DTIC, dacarbazine; HR, hazard ratio; ND, not determined because longer follow-up is needed; NR, not reported; OL, open label; OS, overall survival; PFS, progression-free survival; R, randomized; Tx, treatment.

<sup>a</sup>Stage IV melanoma; BREAK-3 also included unresectable stage III.

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

<sup>c</sup>Median PFS is given in months. OS is given as 1-year rate. Median duration, P value, and hazard ratio were determined using the Kaplan-Meier method. P values are for comparisons with the control arm.

<sup>d</sup>Percentage of patients who experienced any type of treatment-related AE of grade 3 or 4.

<sup>e</sup>Data in parentheses indicate the percentage of patients with BRAF V600K mutation.

<sup>f</sup>Percentage of patients with AEs of grade ≥2. Rates of adverse events of grade ≥3 were not reported.

<sup>g</sup>Patient with active brain metastases were excluded from the trial.

<sup>h</sup>Intracranial duration of response.

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References:

1. NCCN Guidelines Insights
   - BRAF mutation status. The NCCN Melanoma Panel considers all recommended checkpoint immunotherapy options appropriate for both BRAF mutant and BRAF wild-type metastatic disease. There is interest in PD-L1 as a predictive biomarker for response to anti–PD-1 therapy, but to date it has not been discriminant enough to be used to inform treatment decisions in clinical practice.

2. Although ipilimumab is FDA-approved for the 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 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.

3. Selection between anti–PD-1 monotherapy and nivolumab/ipilimumab combination therapy should be informed by the consideration that although combination therapy has been shown to provide somewhat better PFS, it is associated with a much higher risk of serious immune-mediated toxicities, and there is currently no evidence of improvement in OS. 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 adverse events.

4. For patients with BRAF-mutant metastatic disease, BRAF-targeted first-line therapy options include BRAF/MEK inhibitor combination therapy.
with dabrafenib/trametinib or vemurafenib/cobimetinib, or single-agent BRAF inhibitor therapy with vemurafenib or dabrafenib. All of these regimens are category 1 recommendations based on results from phase III trials in the first-line setting (BRIM-3, BREAK-3, COMBI-d, COMBI-v, Co-BRIM). Both vemurafenib and dabrafenib are FDA-approved as single-agent therapy for the treatment of patients with metastatic or unresectable melanoma with BRAF V600E mutation as detected by an FDA-approved test.\(^4\)\(^5\)\(^6\) Dabrafenib/trametinib and vemurafenib/cobimetinib combination therapy regimens are FDA-approved for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations, as detected by an FDA-approved test.\(^4\)\(^5\)\(^6\) The Cobas 4800 BRAF V600E 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 Melanoma Panel recommends that BRAF mutational status be tested using an FDA-approved test or by a CLIA-approved facility. The NCCN Melanoma Panel recommends that tissue for genetic analysis be obtained either from biopsy of a metastasis (preferred) or from archival material. The panel considers single-agent BRAF inhibitor monotherapy and BRAF/MEK inhibitor combination therapy appropriate treatment options for metastatic disease with any type of activating BRAF mutation (includes V600E, V600K, V600R, V600D, and others). Although trametinib is FDA-approved for single-agent use to treat patients with unresectable or metastatic melanoma with BRAF V600E mutation,\(^4\) trametinib monotherapy

### Table 8. BRAF/MEK Inhibitor Combination in Advanced Melanoma: Key Trials

<table>
<thead>
<tr>
<th>Name(^a)</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Phase, Design</th>
<th>BRAF V600E (K)</th>
<th>Brain Mets</th>
<th>Treatment Arms</th>
<th>Response(^d)</th>
<th>AE Grade ≥3(^f)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRIM-3(^a),(^b)</td>
<td>NCT01271803</td>
<td>Ib, OL</td>
<td>49% (93%)</td>
<td>NR(^d)</td>
<td>Vem + cobi, dose escalation: BRAFi-naïve (n=63) 87%</td>
<td>1.4</td>
<td>17%</td>
</tr>
<tr>
<td>NCT01072175(^a),(^b)</td>
<td>I/II, OL</td>
<td>86% (14%)</td>
<td>Dab + tram (n=71) 14%</td>
<td>NR</td>
<td>7.8</td>
<td>3.6</td>
<td>10–11.8</td>
</tr>
<tr>
<td>COMBI-d(^c)</td>
<td>NCT01584648</td>
<td>III, RDB</td>
<td>100% (85%)</td>
<td>NR(^d)</td>
<td>Dab + tram (n=211) 69%</td>
<td>12.9</td>
<td>11.0</td>
</tr>
<tr>
<td>COMBI-v(^d)</td>
<td>NCT01597908</td>
<td>III, OL</td>
<td>100% (90%)</td>
<td>NR(^d)</td>
<td>Dab + tram (n=352) 64%</td>
<td>13.8</td>
<td>11.4</td>
</tr>
<tr>
<td>Co-BRIM(^e)</td>
<td>NCT01689519</td>
<td>III, RDB</td>
<td>100% (70%)</td>
<td>1% (^j)</td>
<td>Vem + cobi (n=247) 68%</td>
<td>1.8</td>
<td>ND</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vem + pbo (n=248) 45%</td>
<td>1.8</td>
<td>7.3</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; BRAF V600E, percentage of patients with the V600E BRAF mutation; Brain mets, percentage of patients with brain metastases at baseline; BRAF-naïve, patients without prior BRAF inhibitor treatment; Dab, dabrafenib; cobi, cobimetinib; mets, metastases; NR, not reported; OL, open-label; OS, overall survival; pbo, placebo; PFS, progression-free survival; R, randomized; RDB, randomized double blind; tram, trametinib; Tx, treatment; vem, vemurafenib.

\(^a\)Unresectable stage III or IV melanoma.

\(^b\)Patients with previously untreated advanced disease.

\(^c\)Data in parenthesis indicate the percentage of patients with BRAF V600K mutation.

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

\(^e\)Median PFS and median OS are given in months. Median durations and \(P\) value are per Kaplan-Meier analysis. \(P\) values are for comparisons with the control arm.

\(^f\)Percentage of patients with AE of any cause (treatment or otherwise).

\(^g\)Patients with active brain mets were excluded from the trial.

\(^h\)Patients who had recently progressed on vemurafenib.

\(^i\)AE rates depended on dose.

\(^j\)All patients progressed on prior BRAF inhibitor.

\(^k\)Treatment-related AEs.

\(^l\)All patients had BRAF V600 mutation, but for 20% the exact mutation was unknown.

\(^m\)Median OS was not reached for either arm; 9-month survival rates are shown.

Table 9. NCCN Recommended Dosing Regimens

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Recommended Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab</td>
<td>3 mg/kg Q3W for up to 4 doses</td>
</tr>
<tr>
<td>Nivolumab monotherapy</td>
<td>3 mg/kg Q2W for up to 2 years</td>
</tr>
<tr>
<td>Nivolumab combination therapy (with ipilimumab)</td>
<td>1 mg/kg Q3W for 4 doses, then 3 mg/kg Q2W for up to 2 years</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>2 mg/kg Q3W for up to 2 years</td>
</tr>
</tbody>
</table>

Abbreviations: Q2W, once every 2 weeks; Q3W, once every 3 weeks.

is no longer an NCCN-recommended treatment option due to relatively poor efficacy compared with BRAF inhibitor monotherapy and BRAF/MEK inhibitor combination therapy. Among the recommended BRAF-targeted therapy options, the BRAF/MEK inhibitor combination is preferred over BRAF inhibitor monotherapy based on results from phase III trials in the first-line setting showing improved outcomes and similar risk of toxicity (COMBI-d, COMBI-v, and CoBRIM).

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

Second-Line or Subsequent Systemic Therapy

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

In addition to the checkpoint immunotherapy regimens recommended for first-line, second-line, and subsequent treatment of metastatic disease, single-agent ipilimumab is an option in patients who have received prior systemic therapy for metastatic disease. This recommendation is based on the results from the pivotal phase III trial (CA184-002) in patients with previously treated unresectable stage III or IV melanoma. Of the recommended options for second-line and subsequent therapy, the NCCN Melanoma Panel recommends considering only those agents that are not the same or of the same class as the agents the patient received previously. Patients treated with ipilimumab who experience stable disease of 3 months’ duration after week 12 of induction or partial or complete response, who subsequently experience progression of melanoma, may be offered reinduction with up to 4 doses of ipilimumab at 3
mg/kg Q3W. Although anti–CTLA-4 (ipilimumab) and anti–PD-1 (nivolumab, pembrolizumab) agents are both checkpoint immunotherapies, they are not considered the same class of agent because they target different molecules. For patients who previously received ipilimumab, subsequent treatment with anti–PD-1 therapy is a recommended option, and vice versa. Patients whose disease previously progressed or who achieved maximal response on BRAF inhibitor therapy are unlikely to benefit from BRAF/MEK combination therapy. Likewise, patients whose disease progressed or achieved maximal response on BRAF/MEK combination therapy are unlikely to respond to BRAF monotherapy or a different BRAF/MEK combination. For patients who have progressed on checkpoint immunotherapies (and BRAF-targeted therapy if BRAF-mutated), additional options to consider for second-line or subsequent therapy include high-dose interleukin-2, biochemotherapy (category 2B), cytotoxic agents, and imatinib for tumors with activating mutations of C-KIT. It is not known which of these options may provide benefit, because data supporting these approaches largely predate the development checkpoint inhibitor and BRAF-targeted therapies.

**Immune Checkpoint Inhibitor Administration**

Ipilimumab is FDA-approved for the treatment of unresectable or metastatic melanoma at a dose of 3 mg/kg of body weight, administered Q3W for a total of 4 doses, consistent with the dosing regimen in the phase III trials described. The NCCN Melanoma Panel recommend the use of ipilimumab at the FDA-approved dose and schedule.

As described earlier, FDA-recommended dosing regimens indicate that treatment should continue until disease progression or unacceptable toxicity for all 3 of the approved regimens containing anti–PD-1 agents: nivolumab, pembrolizumab, and nivolumab/ipilimumab combination therapy. Due to the lack of data on long-term anti–PD-1 treatment, the optimal treatment duration is unknown. In the absence of unacceptable toxicity, it is common practice to continue anti–PD-1 therapy until maximal response. Although there is no standard definition for maximal response, it is commonly defined as no additional tumor regression on at least 2 consecutive scans taken at least 12 weeks apart. Treatment after maximal response is controversial. Continuing anti–PD-1 treatment for one 12-week cycle after maximal response has been achieved is not uncommon in clinical practice. NCCN-recommended dosing regimens are listed in Table 9.

**Summary**

The NCCN Guidelines for Melanoma represent an effort to distill and simplify an enormous body of knowledge and experience into fairly simple management algorithms. These guidelines are intended as a point of departure, recognizing that all clinical decisions about individual patient management must be tempered by the clinician’s judgment and other factors, such as local resources and expertise as well as the individual patient’s needs, wishes, and expectations. Systemic therapies for treatment of metastatic disease are all associated with considerable risk of toxicity, and treatment decisions should be informed by consideration of these risks and assessment of factors that may increase risk of toxicity. Please see the full NCCN Guidelines for Melanoma (available at www.NCCN.org) for a summary of safety data and recommendations for risk assessment, monitoring, detection, prevention, and management of toxicities in patients receiving systemic therapy for metastatic melanoma.

**References**


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Posttest Questions
1. A patient presents with disseminated unresectable metastatic disease without brain metastases, confirmed through biopsy and positive for BRAF V600E mutation. Which of the following immunotherapies are NCCN-recommended first-line systemic therapy options for this patient?
   1. Ipilimumab
   2. Pembrolizumab
   3. Nivolumab
   4. Nivolumab/ipilimumab combination
   5. Pembrolizumab/ipilimumab combination
   Answer Choices:
   A: 1, 3, and 4
   B: 1, 2, and 5
   C: 2, 3, and 4
   D: All of the above

2. Which of the following targeted therapies are preferred first-line systemic therapy options for this patient?
   A. Monotherapy with dabrafenib or vemurafenib
   B. Dabrafenib monotherapy or dabrafenib/trametinib combination
   C. Vemurafenib monotherapy or vemurafenib/cobimetinib combination
   D. Dabrafenib/trametinib or vemurafenib/cobimetinib combination

3. True or False: The patient elects to have treatment with dabrafenib monotherapy therapy. After an initial response that lasts approximately 6 months, the disease progresses. Because the patient showed an initial good response to dabrafenib, a BRAF/MEK inhibitor combination is a good option for her.