MELANOMA TREATMENT REGIMENS (Part 1 of 4)

Clinical Trials: The NCCN recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any 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 makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Systemic Therapy Options for Metastatic or Unresectable Melanoma[1]

Note: All recommendations are category 2A unless otherwise indicated.

REGIMEN	DOSING
First-line Immunotherapy Regimens	
Nivolumab (Category 1)[2,3abcd]	Nivolumab 3mg/kg IV every 2 weeks.
Nivolumab + ipilimumab[4,5abcdef]	**Day 1:** Nivolumab 1mg/kg followed by ipilimumab 3mg/kg IV every 3 weeks for 4 cycles; then, nivolumab 3mg/kg every 2 weeks.
Pembrolizumab[6-9acd]	Pembrolizumab 2mg/kg IV every 2 weeks.
First-line Targeted Therapy for BRAF-Mutant Melanoma	
Preferred Regimens	
Dabrafenib + trametinib (Category 1)[10-13ghi]	Dabrafenib 150mg orally twice daily + trametinib 2mg/day orally.
Vemurafenib + cobimetinib (Category 1)[14-16ghij]	Vemurafenib 960mg orally twice daily on days 1–28 + cobimetinib 60mg/day orally on days 1–21. Repeat cycle every 28 days.
Other Active Regimens	
Vemurafenib (Category 1)[17,18ghi]	Vemurafenib 960mg orally twice daily.
Dabrafenib (Category 1)[19,20ghi]	Dabrafenib 150mg orally twice daily.
Second-line or Subsequent Therapy[k]	
Pembrolizumab[6-9acdl]	Pembrolizumab 2mg/kg IV every 2 weeks.
Nivolumab[2,3abcd]	Nivolumab 3mg/kg IV every 2 weeks.
Nivolumab + ipilimumab[4,5abcdefl]	**Day 1:** Nivolumab 1mg/kg followed by ipilimumab 3mg/kg IV every 3 weeks for 4 cycles; then, nivolumab 3mg/kg every 2 weeks.
Ipilimumab (Category 1)[21-24cdelm]	**Day 1:** Ipilimumab 3mg/kg IV. Repeat cycle every 3 weeks for 4 cycles.
High-dose IL-2[5-28no]	**Days 1–5:** IL-2 22mcg/kg (360,000 IU/kg), 33mcg/kg (540,000 IU/kg), 36mcg/kg (600,000 IU/kg), or 44mcg/kg (720,000mcg/kg) IV every 8 hours for up to 14 consecutive doses as clinically tolerated.
Dacarbazine[29]	**Day 1:** Dacarbazine 2–4.5mg/kg/day IV for 10 days. Repeat cycle every 4 weeks. **OR** **Days 1–5:** Dacarbazine 250mg/m^2/day IV. Repeat cycle every 3 weeks.
Temozolomide[30]	**Days 1–5:** Temozolomide 200mg/m^2/day orally for 5 days. Repeat cycle every 4 weeks.
Paclitaxel[31]	Paclitaxel 250mg/m^2 continuous IV infusion for 24 hours. Repeat cycle every 21 days.
Albumin-bound paclitaxel[32,33]	Nab-paclitaxel 100mg/m^2 (in previously treated patients) or 150mg/m^2 (in chemotherapy-naive patients) IV. Repeat every week for 3–4 cycles.
Carboplatin + paclitaxel[34-37]	**Days 1, 8, and 15:** Paclitaxel 100mg/m^2 IV + carboplatin (AUC = 2) IV. Repeat cycle every 4 weeks until disease progression
Biochemotherapy for metastatic disease (Category 2B)[38-42o]	Dacarbazine or temozolomide, + cisplatin or carboplatin, ± vinblastine or nitrosourea, + IL-2 + IFN-alpha-2b

continued

MELANOMA TREATMENT REGIMENS (Part 2 of 4)

Systemic Therapy Options for Metastatic or Unresectable Melanoma[1] (continued)

Second-line or Subsequent Therapy[k] (continued)

REGIMEN	DOSING
Biochemotherapy for adjuvant treatment of high-risk disease (Category 2B)[43o]	Dacarbazine, cisplatin, vinblastine, IL-2, and interferon alfa-2b
Imatinib[44,45p]	Imatinib 400mg orally twice daily.
Talimogene laherparepvec (T-VEC)[46q]	Recommended starting dose is up to a maximum of 4 mL of T-VEC at a concentration of 106 (1 million) plaque-forming units (PFU) per mL. Subsequent doses should be administered up to 4 mL of T-VEC at a concentration of 108 (100 million) PFU per mL.

Second-Line or Subsequent Therapy for BRAF-Mutant Melanoma

Preferred Regimens

Dabrafenib + trametinib[10-13ghi]	Dabrafenib 150mg orally twice daily + trametinib 2mg/day orally.
Vemurafenib + cobimetinib[14-16ghij]	Vemurafenib 960mg orally twice daily on days 1–28 + cobimetinib 60mg/day orally on days 1–21. Repeat cycle every 28 days.

Other Active Regimens

Vemurafenib[17,18ghi]	Vemurafenib 960mg orally twice daily.
Dabrafenib[19,20ghi]	Dabrafenib 150mg orally twice daily.

[a] Nivolumab or pembrolizumab may cause immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hyperthyroidism. For moderate to severe immune-mediated toxicities, discontinue therapy and administer systemic steroids.

[b] Clinically significant (grade 3 and 4) immune-related adverse events are seen more commonly with nivolumab/ipilimumab combination therapy compared with iplimumab or nivolumab monotherapy. This emphasizes the need for careful patient education, selection, and monitoring.

[c] Immune-mediated dermatitis sometimes responds to topical corticosteroids. For patients who do not respond, consider referral to a dermatologist or provider experienced in diagnosing and management cutaneous manifestations of immunotherapy.

[d] Infliximab 5 mg/kg is preferred for treatment of severe immune-related colitis that does not resolve with high-dose steroids. A single dose of infliximab is sufficient to resolve immune-related colitis in most patients.

[e] Ipilimumab has the potential for significant immune-mediated complications. Although no longer required by the FDA, the Risk Evaluation and Mitigation Strategy program and/or experience in use of the drug as well as resources to follow the patient closely are essential for safe use of ipilimumab. It should be used with extreme caution, if at all, in patients with underlying immune disorders.

[f] Nivolumab/ipilimumab combination therapy was associated with better relapse-free survival than either agent used alone in a phase 3 trial, but the combination significantly increased toxicity. The combination's effect on overall survival (OS) is undetermined.

[g] Vemurafenib, dabrafenib, and trametinib are recommended only for patients with V600 mutation of the BRAF gene documented by an FDA-approved or Clinical Laboratory Improvement Amendments (CLIA)-approved facility.

[h] Regular dermatologic evaluation and referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of targeted therapy is recommended. BRAF inhibitors are associated with cutaneous squamous cell carcinoma, extreme photosensitivity, and other dermatologic toxicities, which occur much less often with concurrent MEK inhibitors.

[i] Pyrexia (defined as a temperature of 38.5°C or greater) is a common (~55%) side effect of combining BRAF and MEK inhibitors and occurs less frequently with BRAF monotherapy (~20%). The pyrexia is episodic, and onset is often 2 to 4 weeks following the start of therapy with a median duration of 9 days. Pyrexia may be associated with chills, night sweats, rash, dehydration, electrolyte abnormalities, and hypotension. Stopping or holding dabrafenib and trametinib at the onset of pyrexia will often interrupt the episode, and treatment can be resumed with full-dose dabrafenib and trametinib upon cessation of pyrexia and pyrexia-related symptoms. Upon re-exposure to dabrafenib and trametinib, repeat pyrexia events can occur, but grade >3 events are uncommon (21%). In occasional instances of prolonged or severe pyrexia not responsive to discontinuation of dabrafenib and trametinib, low-dose steroids (prednisone 10 mg/day) can be used. Patients with pyrexia should be advised to use antipyretics as needed and increase fluid intake.

[j] Vemurafenib/cobimetinib combination therapy was associated with better PFS and a better response rate than vemurafenib monotherapy in previously untreated patients with unresectable stage IIIC or stage IV disease. The combination's effect on OS compared to single-agent vemurafenib is unknown.

[k] Consider second-line agents that were not used in first-line therapy and that are not of the same class.

[l] For patients with preexistent hypophysitis due to iplimumab, pembrolizumab may be administered if patients are on appropriate physiologic replacement endocrine therapy.

[m] Ipilimumab reintroduction may be considered for select patients who did not experience significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or have progression after stable disease > 3 months.

[n] High-dose IL should not be used in patients with inadequate organ reserve, poor performance status, or untreated or active brain metastases. IL-2 may be considered for patients with small brain metastases and without significant peritumoral edema.

[o] Administration of multiagent regimens and high-dose IL-2 is complex and associated with significant toxicities. Therapy should only be administered at an institution with medical staff experienced in the administration and management of these regimens.

[p] For tumors with activating mutations of C-KIT.

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