MELANOMA TREATMENT REGIMENS (Part 1 of 3)

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 Advanced Or Metastatic Melanoma[1]

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

Preferred Regimens

REGIMEN	DOSING
Ipilimumab (Category 1)[2-5∗†‡]	**Day 1:** Ipilimumab 3mg/kg IV once. Repeat cycle every 3 weeks for 4 cycles.
Dabrafenib + trametinib (Category 1)[6-8‡§‖]	Dabrafenib 150mg PO twice daily + trametinib 2mg PO once daily.
Pembrolizumab[9,10‡¶#]	Pembrolizumab 2mg/kg IV every 3 weeks.
Nivolumab[11¶Δ]	Nivolumab 3mg/kg IV every 2 weeks.

Other Active Regimens

Vemurafenib (Category 1)[12,13‡§◊]	Vemurafenib 960mg PO twice daily.
Dabrafenib (Category 1)[14,15‡§□]	Dabrafenib 150mg PO twice daily.
Trametinib (Category 1)[16‡§∂]	Trametinib 2mg PO once daily.
Imatinib[17,18←]	Imatinib 400mg PO twice daily.
Dacarbazine[19]	**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[20]	**Days 1–5:** Temozolomide 200mg/m^2/day PO for 5 days. Repeat cycle every 4 weeks.
Albumin-bound paclitaxel[21,22]	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.
High-dose IL-2[23-26‡↑→↓]	**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.
Cisplatin + vinblastine + dacarbazine + IL-2 + IFN-alpha (Category 2B)[27→]	**Day 1:** Dacarbazine 800mg/m^2 IV **Days 1–4:** Cisplatin 20mg/m^2 IV daily + vinblastine 1.6mg/m^2 IV daily + IL-2 9×10^6 IU/m^2 continuous IV infusion daily **Days 1–5:** IFN-alpha 5×10^6 U/m^2 SC daily. Repeat cycle every 21 days.
Cisplatin + vinblastine + dacarbazine ± IL-2 + IFN-alpha[28,29→]	**Days 1–4 and 22–25:** Cisplatin 20mg/m^2 IV + vinblastine 2mg/m^2 (1.5mg/m^2 when given with biochemotherapy) IV **Days 1 and 22:** Dacarbazine 800mg/m^2 IV, **±** **Days 5–8, 17–20, and 26-29:** IL-2 9x106 IU/m^2 continuous IV infusion **Days 5–9, 17–21, and 26-30:** IFN alfa-2b 5×10^6 U/m^2 SC.
Paclitaxel (Category 2B)[30]	Paclitaxel 250mg/m^2 continuous IV infusion for 24 hours. Repeat cycle every 21 days.
Paclitaxel + carboplatin (Category 2B)[31-34]	**Days 1, 8, and 15:** Paclitaxel 100mg/m^2 IV + carboplatin AUC 2 IV. Repeat cycle every 4 weeks until disease progression.

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Systemic Therapy Options For Advanced Or Metastatic Melanoma[1] (continued)

[*] Ipilimumab has the potential for significant immune-mediated complications. Participation in the risk evaluation and mitigation strategy (REMS) program and/or experience in use of the drug as well as resources to follow the patient closely are essential. Ipilimumab should be used with extreme caution, if at all, in patients with serious underlying autoimmune disorders.

[†] Re-induction with ipilimumab may be considered for select patients who experienced no significant systemic toxicity during prior ipilimumab therapy and who relapse after initial clinical response or progress after stable disease >3 months.

[‡] Regular dermatologic evaluation and referral to a dermatologist or provider experienced in the diagnosis and management of cutaneous manifestations of targeted therapy and/or immunotherapy is recommended. Patients should also be educated to report the development of other adverse reactions such as joint pain and swelling.

[§] 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.

[‖] The combination of dabrafenib and trametinib was associated with improved progression-free survival (PFS) compared to dabrafenib monotherapy in a phase I/II trial; however, improvement in overall survival has not been demonstrated. Combination therapy may be associated with less cutaneous toxicity than monotherapy, but systemic toxicity may be increased.

[¶] While pembrolizumab and nivolumab are indicated for disease progression after treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, there is consensus among the NCCN panel that both drugs have higher response rates and less toxicity compared to ipilimumab, and that both drugs should be included as options for first-line treatment.

[#] Pembrolizumab may cause immune-mediated adverse reactions. Depending on the severity of the reaction, pembrolizumab should be discontinued and corticosteroids administered for immune-mediated: pneumonitis, colitis, hepatitis, hypophysitis, nephritis, and hyperthyroidism. For patients with pre-existent hypophysitis due to ipilimumab, pembrolizumab may be administered if patients are on appropriate physiologic replacement endocrine therapy.

[Δ] Nivolumab may cause immune-mediate adverse reactions, including pneumonitis, colitis, hepatitis, nephritis, hypothyroidism, and hyperthyroidism. Depending on the adverse event and the severity of the reaction, discontinuation of therapy and administration of corticosteroids may be required.

[◊] Vemurafenib has the potential for significant dermatologic complications including cutaneous squamous cell carcinoma and extreme photosensitivity. Regular dermatologic evaluation with referral to a dermatologist is recommended. Patients should also be educated to report the development of other adverse reactions such as joint pain and swelling.

[□] Dabrafenib administration can be associated with significant episodic and recurrent fevers that should be managed by discontinuation of dabrafenib and institution of anti-pyretics such as acetaminophen and/or NSAIDs. Dabrafenib is associated with keratoacanthoma/low grade squamous carcinomas and less photosensitivity than vemurafenib.

[a] Single-agent trametinib is not indicated for the treatment of patients who have experienced progression of disease on prior BRAF inhibitor therapy. Single-agent trametinib can be used for the treatment of BRAF-mutated melanoma in patients who are intolerant to single-agent BRAF inhibitors.

[←] For C-KIT mutated tumors.

[↑] 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).

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

[↓] In the clinical trial setting, a second identical treatment cycle was scheduled after 6 to 9 days of rest, and courses could be repeated every 6 to 12 weeks in stable or responding patients for up to five courses [two cycles/course].

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