

Ipilimumab Monotherapy for Melanoma

An HCP Tool From the Immuno-Oncology Essentials Initiative

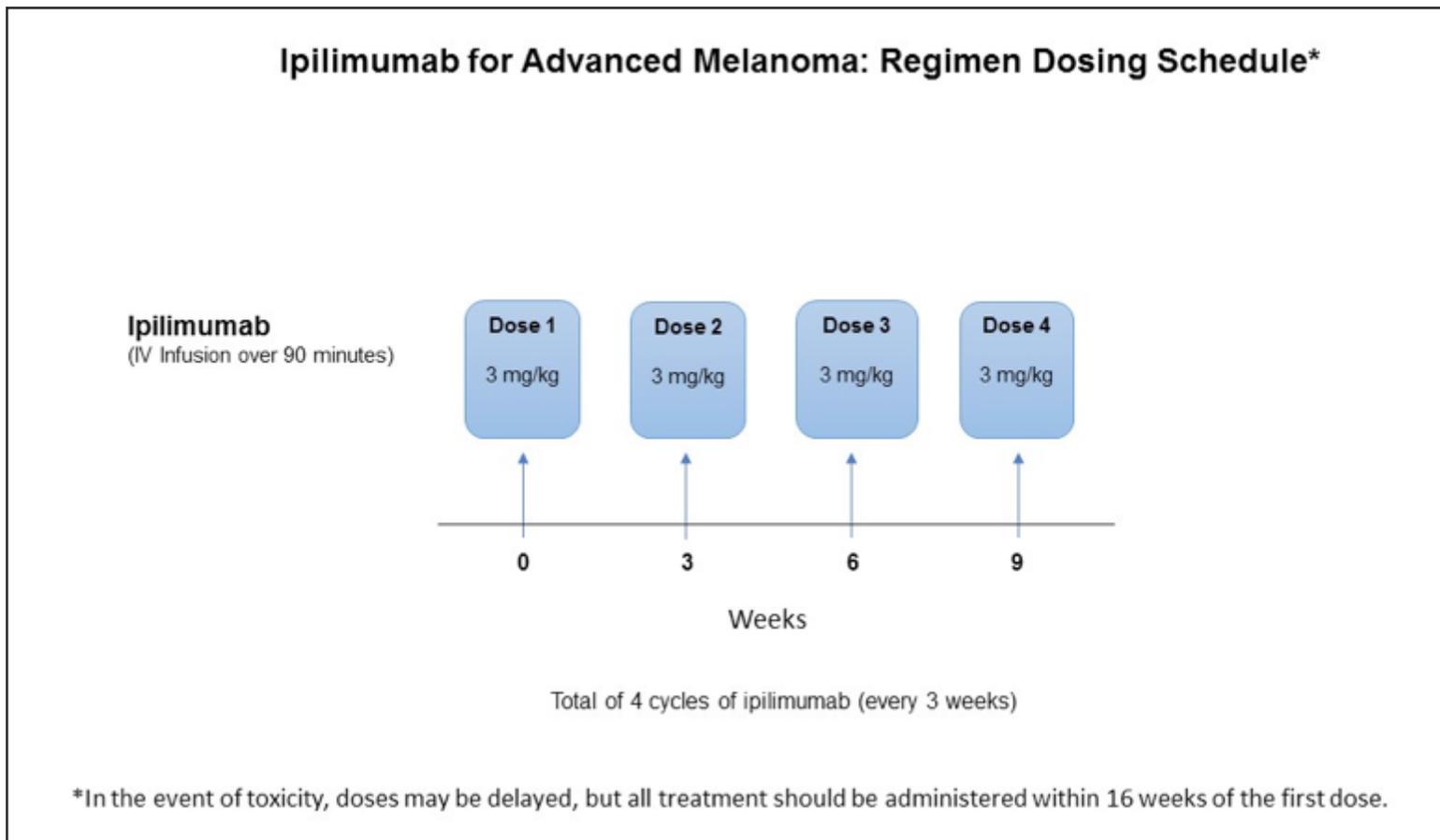
Ipilimumab (Yervoy®) is a monoclonal antibody directed against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), one of the checkpoints that regulates the immune system. CTLA-4 is a negative regulator of T-cell activation and proliferation, which means that it turns the immune response “off.” Ipilimumab binds to CTLA-4, essentially cutting the brake, thereby enabling the immune system to remain “on” and better attack developing cancers.

Ipilimumab is indicated as a monotherapy for unresectable or metastatic (advanced) melanoma and as an adjuvant treatment of resected stage 3 melanoma. Ipilimumab is also indicated in combination with nivolumab (Opdivo®) for the treatment of unresectable or metastatic melanoma (discussed in a separate nursing tool).

This document is part of an overall HCP toolkit intended to assist providers in optimizing management of melanoma patients receiving newer anti-melanoma therapies.

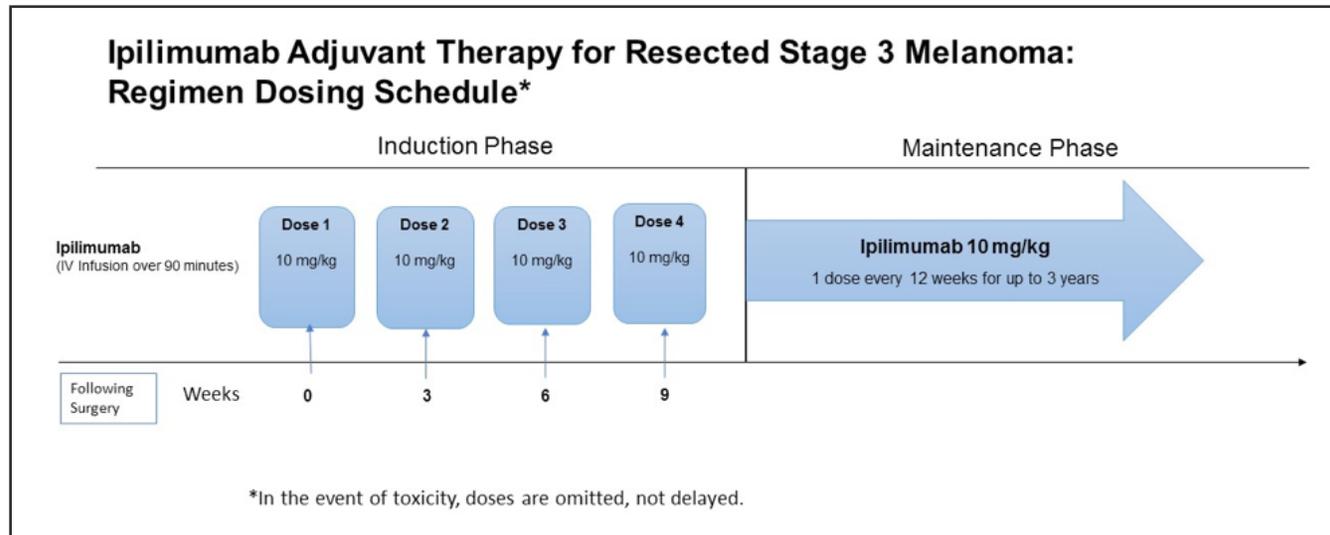
DRUG DOSAGE/ADMINISTRATION

- A higher ipilimumab dose and longer treatment duration is employed when ipilimumab is used as an adjuvant therapy than as a monotherapy for advanced melanoma. The regimens are indicated below:



DRUG DOSAGE/ADMINISTRATION

(CONTINUED)



- Obtain pretreatment laboratory tests (eg, adrenal function [ACTH], clinical chemistries, liver function tests, and thyroid function tests) prior to initiation of therapy and before each cycle
- Ipilimumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if solution is cloudy, discolored, or contains extraneous particulate matter (other than a few translucent-to-white, proteinaceous particles)
- Do not shake the vial and do not coadminister ipilimumab with other drugs through the same intravenous line. It is important to assure IV access before administration. Administer ipilimumab through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line filter (we recommend a pore size of 0.2–4 micrometers)

Note: A phase 3 study report from ASCO 2017 indicated an adjuvant ipilimumab dose of 10 mg/kg was associated with higher rates of treatment-related adverse events than a lower 3-mg/kg dose in patients with resected high-risk melanoma, without improving recurrence-free survival.

SIDE EFFECTS AND THEIR MANAGEMENT

Because ipilimumab is an immunotherapy that works by enhancing the patient’s immune system, most adverse reactions associated with ipilimumab are related to overactivity of the patient’s immune system (ie, immune-related adverse events [irAEs]). Various organ systems (often more than one) or tissues may be affected.

- Keys to toxicity management:
 - » Proactive assessment for early signs/symptoms of toxicity
 - » Prompt intervention
 - » irAEs are typically managed with dose interruption and selective use of corticosteroids
 - » In rare instances, toxicity may be steroid refractory, and additional immunosuppressive agents may be necessary (infliximab, mycophenolate mofetil, cyclophosphamide, etc)
 - » Ipilimumab may be held or discontinued depending on severity and/or persistence
 - » Referral to organ specialist should be considered
- irAEs associated with ipilimumab treatment can be categorized into those that are most common, less common but serious, and others that are easily overlooked
- Table 1 lists these irAEs and the corresponding Care Step Pathways in Appendix 1. Other adverse events associated with ipilimumab are shown in Appendix 2

Table 1. Care Step Pathways for the Management of Immune-Related AEs Associated With Ipilimumab Monotherapy

irAE category	Examples	Location
Most common	Skin toxicities (pruritis, rash, etc) Gastrointestinal toxicity: Diarrhea and colitis Thyroiditis Hepatic toxicities	Appendix 1
Less common but serious	Additional endocrinopathies - Hypophysitis (pituitary) - Adrenal insufficiency (adrenalitis) - Diabetes Pneumonitis	Appendix 1
Easily overlooked	Arthralgia/arthritis Mucositis/xerostomia Neuropathy Nephritis	Appendix 1

CLINICAL PEARLS

- It is important to monitor laboratory values at the start of treatment, periodically during treatment, and as indicated clinically. Laboratory values commonly monitored include: CBC w/ differential, creatinine, alkaline phosphatase, AST/ALT, bilirubin (direct/total), sodium, potassium, calcium, magnesium, thyroid function, and glucose. See individual irAE CSPs for more specific laboratory monitoring guidelines
- Ipilimumab-related irAEs may occur at any time, including after treatment completion or discontinuation. Continuing to monitor patients is critical
- Patients sometimes experience signs/symptoms that they think are due to “flu” or a cold, but that actually represent an irAE or an infusion reaction
- Endocrinopathies often present with vague symptoms (fatigue, headache, and/or depression) that can easily be overlooked or initially misdiagnosed. Hypervigilance and follow-up is important on the part of both nurses and patients
- Unlike other irAEs, endocrinopathies usually do not resolve and may require lifelong hormone replacement therapy
- IrAEs may become apparent upon tapering of corticosteroids, since they can be suppressed or masked by immunosuppressive therapy. Patients should be advised to be on the lookout for early signs of irAEs during the tapering period
- HCPs should encourage patients to carry information about their ipilimumab regimen with them at all times. This might be the ipilimumab-specific wallet card, or at least emergency phone numbers and the side effects associated with the regimen. You may suggest that they paperclip the wallet and insurance cards together so information about their regimen will be shared whenever they show their insurance card
- Advise patients to take pictures of any skin changes for documentation

QUESTIONS & ANSWERS

Q. Is ipilimumab monotherapy still being used in the advanced melanoma setting?

A. Yes. While PD-1 inhibitors and the combination of ipilimumab and nivolumab are more typically used, there are some patients who still receive ipilimumab monotherapy for unresectable or metastatic melanoma. In fact, the ipilimumab label was recently expanded to include use in pediatric patients age 12 and older with advanced melanoma.

Q. How do I counsel my patients about immunizations?

A. That's a logical question, given that the checkpoint inhibitors alter the immune response. Advise your patients not to receive live vaccines (eg, measles, mumps, and rubella and the varicella vaccine [Zostavax[®]]) because they have not been evaluated in this setting. The use of attenuated vaccines has been and continues to be evaluated. Counsel patients to discuss all immunizations with the oncology team prior to administration so the benefits and risks can be weighed on an individual basis. For example, SHINGRIX[®], approved in 2017, is an attenuated (non-live) varicella vaccine; its use can be discussed with the oncology team if a recommendation is being made for the patient to receive the injection series. Annual influenza vaccination with the inactivated influenza vaccine is recommended. The nasal spray flu vaccine is a live attenuated influenza vaccine and should not be administered to patients treated with immune checkpoint inhibitors.

PATIENT RESOURCES

Financial Assistance

BMS Access Support

1 (800) 861-0048

<http://www.bmsaccesssupport.bmscustomerconnect.com/patient>

Additional Information Resources

AIM at Melanoma Foundation (Nurse on Call, patient symposia, drug resources, etc)

<http://www.AIMatMelanoma.org>

American Cancer Society Resource Section

<https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/immunotherapy/immune-checkpoint-inhibitors.html>

ADDITIONAL RESOURCES

- Boutros C, Tarhini A, Routier E, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol*. 2016;13:473-486.
- Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2018;36:1-60.
- Dadu R, Zobniw C, Diab A. Managing adverse events with immune checkpoint agents. *Cancer J*. 2016;22:121-129.
- Food and Drug Administration & Bristol-Myers Squibb. Risk Evaluation and Mitigation Strategy (REMS) for ipilimumab (Yervoy); February 2012. Includes wallet card etc. Available at: <https://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM249435.pdf>
- Friedman CF, Proverbs-Singh TA, Postow MA. Treatment of the immune-related adverse effects of immune checkpoint inhibitors: a review. *JAMA Oncol*. 2016;2:1346-1353.
- Madden KM, Hoffner B. (2017). Ipilimumab-based therapy: consensus statement from the faculty of the Melanoma Nursing Initiative on managing adverse events with ipilimumab monotherapy and combination therapy with nivolumab. *Clin J Oncol Nurs*. 2017;21(suppl):30-41.
- National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology: Management of Immunotherapy-Related Toxicities. Version 1.2018. Fort Washington, PA: National Comprehensive Cancer Network; 2018.
- Rubin KM. Managing immune-related adverse events to ipilimumab: a nurse's guide. *Clin J Oncol Nurs*. 2012;16:E69-E75.
- Villadolid J, Amin A. Immune checkpoint inhibitors in clinical practice: update on management of immune-related toxicities. *Transl Lung Cancer Res*. 2015;4:560-577.
- Yervoy® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2018. Available at: http://packageinserts.bms.com/pi/pi_yervoy.pdf

Click here for downloadable action plans to customize for your patients

APPENDIX 1

The 12 Care Step Pathways (CSPs) referenced in this Appendix are housed in the CSP section of the AIMWithImmunotherapy.com IO Essentials website. These CSP are currently universally applicable (i.e., they don't differ across tumor types).

Please click the link below to access the CSPs, which can also be printed from that section of the site.

<http://aimwithimmunotherapy.org/care-step-pathways/>

APPENDIX 2

Management of other AEs associated with ipilimumab therapy

Adverse event	Common symptoms	Common management/anticipatory guidance
Acute respiratory distress syndrome	Severe shortness of breath, dyspnea, or rapid breathing, hypotension, confusion, and extreme fatigue	<ul style="list-style-type: none"> • Serious condition requiring hospitalization/expert care, including supplemental oxygen, often mechanical ventilation, and fluid management
Anorexia	Decreased appetite	<ul style="list-style-type: none"> • Monitor weight; query patient about appetite/eating habits; advise dietary modification if necessary (should improve with time) • Anticipate standard dose holds/discontinuations* • Consider referral to nutrition services for counseling on best food choices to avoid excessive weight loss
Cardiotoxicity: cardiomyopathy, myocarditis, heart failure	Dyspnea, edema, fatigue, chest pain, arrhythmias, abdominal pain or ascites	<ul style="list-style-type: none"> • Monitor weight, changes in breathing, extremity edema, chest/back/arm/jaw pain, pressure • ECG, Echo, stress test cardiology referral, 2 mg/kg prednisone, discontinue therapy
Embryo-fetal toxicity	—	<ul style="list-style-type: none"> • Advise of risk to fetus and recommend use of effective contraception during treatment and for 3 months after ipilimumab is discontinued • Advise patients to tell HCP immediately if they or their partner suspect they are pregnant while taking therapy
Encephalitis	Headache, fever, tiredness, confusion, memory problems, sleepiness, hallucinations, seizures, stiff neck	<ul style="list-style-type: none"> • New-onset (Grade 2–3) moderate to severe symptoms: rule out infectious or other causes; consult neurologist, obtain brain MRI, and lumbar puncture • Anticipate standard ipilimumab dose holds/discontinuations;* administer corticosteroids at dose of 1–2 mg/kg/d prednisone equivalents (or 2–4 mg/kg if necessary)
Fatigue	Feeling tired; lack of energy	<ul style="list-style-type: none"> • Query patients regarding energy level; evaluate possible contributory factors, including infection, disease progression, and hematological and metabolic abnormalities; standard supportive care • Anticipate standard dose holds/discontinuations* • Fatigue that interferes with ADLs is concerning and should be evaluated for underlying causes, such as possible endocrinopathy
Headache	Head pain	<ul style="list-style-type: none"> • Need to rule out brain metastases, encephalitis, or hypophysitis; otherwise, standard supportive care (should improve with time) • Headache occurring in conjunction with fatigue could be indicative of hypophysitis • Anticipate standard dose holds/discontinuations*

Management of other AEs associated with ipilimumab therapy

(Continued)

Adverse event	Common symptoms	Common management/anticipatory guidance
Infusion reaction	Chills/shaking, back pain, itching, flushing, difficulty breathing, hypotension, fever	<ul style="list-style-type: none"> • For mild/moderate (Grade 1–2) reactions: interrupt or slow rate of infusion; monitor to recovery. • For severe/life-threatening (Grade 3–4) reactions: Discontinue ipilimumab; manage anaphylaxis via institutional protocol; monitor. Premedication with an antipyretic and antihistamine may be considered for future doses
Insomnia	Difficulty falling or staying asleep	<ul style="list-style-type: none"> • Counsel patients on good sleep habits; prescription medications can be used if needed (should improve over time) • May be related to steroid use • Anticipate standard dose holds/discontinuations*
Nausea/vomiting	Vomiting, queasiness, RUQ or LUQ pain	<ul style="list-style-type: none"> • Provide standard supportive care, since it is adequate in most cases • Check LFTs/lipase/amylase if hepatotoxicity or pancreatitis is suspected • Anticipate standard dose holds/discontinuations*
Ocular: conjunctivitis, blepharitis, episcleritis, iritis, ocular myositis, scleritis, uveitis (associated with ipilimumab)	Blurry vision, double vision, or other vision problems, eye pain or redness	<ul style="list-style-type: none"> • Encourage patient to report any eye symptoms immediately • Obtain ophthalmology referral • Anticipate standard dose ipilimumab holds/discontinuations*
Pyrexia	Elevated body temperature	<ul style="list-style-type: none"> • Standard supportive care related to cytokine release • Consider infectious workup for prolonged elevated temperature • Anticipate standard dose holds/discontinuations*
Rhabdomyolysis	Pain, muscle weakness, vomiting, confusion, tea-colored urine	<ul style="list-style-type: none"> • Anticipate dose holds/discontinuations* • Intravenous fluids and corticosteroids (check creatine kinase levels)
Vision changes	Eye redness, pain, blurred vision, photophobia	<ul style="list-style-type: none"> • Test and evaluate for uveitis and episcleritis (by ophthalmologist, preferably) • Urgency of ophthalmology referral increases with grade • G1: continue immunotherapy, use artificial tears • G2: hold immunotherapy; ophthalmic and systemic corticosteroids (under ophthalmologist guidance) • G3 or G4: permanently discontinue immunotherapy; treatment by ophthalmologist to include ophthalmic and systemic corticosteroids

*Withhold ipilimumab for any G2 (moderate) AE, and resume treatment when AE returns to G0 or 1; permanently discontinue for any G3–4 (life-threatening) AE, persistent G2 AE lasting ≥ 6 weeks, or inability to reduce corticosteroid dose to 7.5 mg/d prednisone or equivalent.