Ipilimumab Monotherapy

An HCP Tool From AIM at Immunotherapy

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.

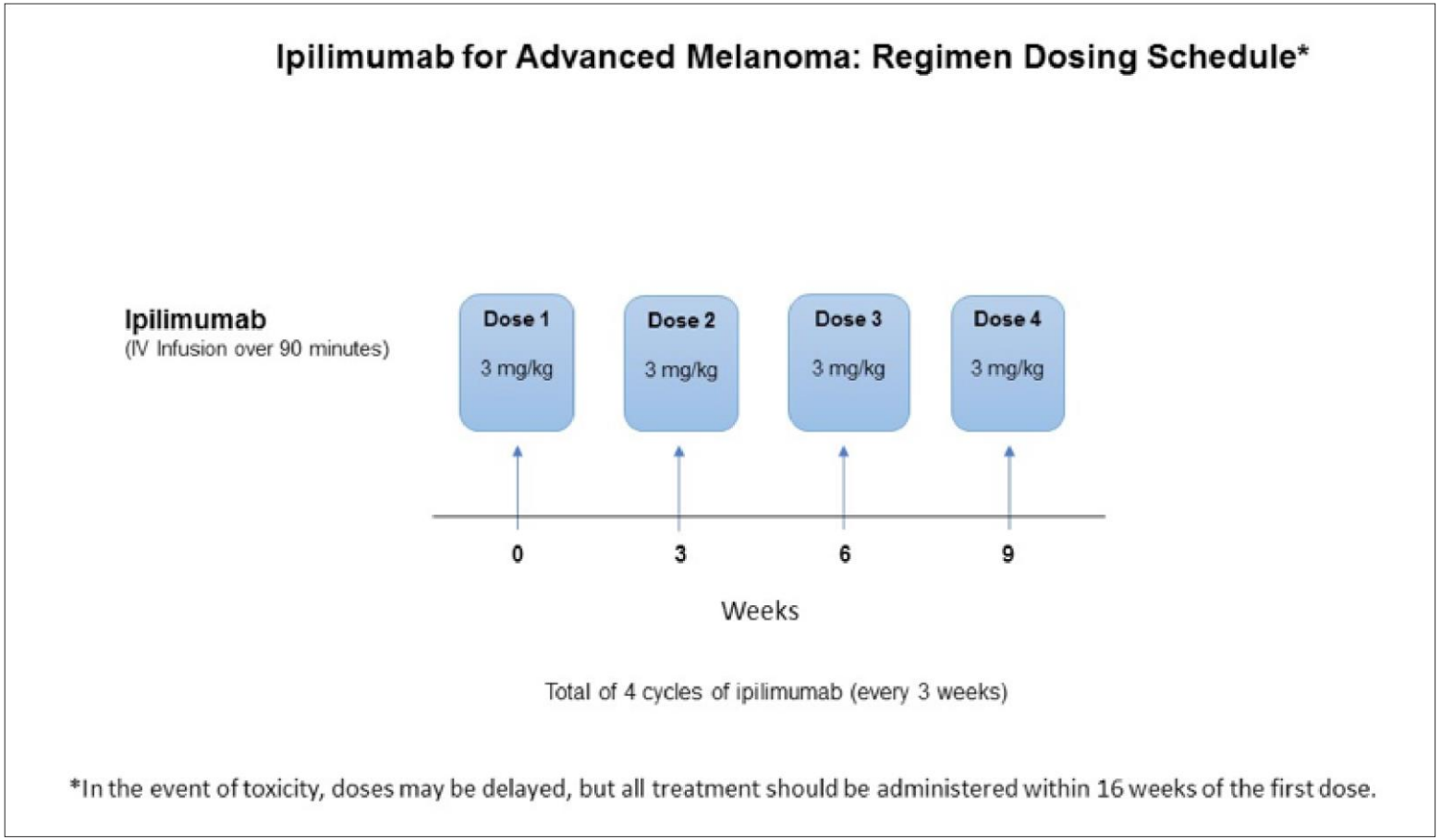
Ipilimumab is indicated as a monotherapy for unresectable or metastatic (advanced) melanoma and as an adjuvant treatment of resected stage 3 melanoma.

Ipilimumab is indicated in combination with nivolumab (Opdivo®) for the treatment of many types of cancers. The combination is discussed in a separate tool (i.e. “ipi/nivo”).

This document is part of an overall HCP toolkit intended to assist providers in optimizing management of patients receiving this therapy.

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

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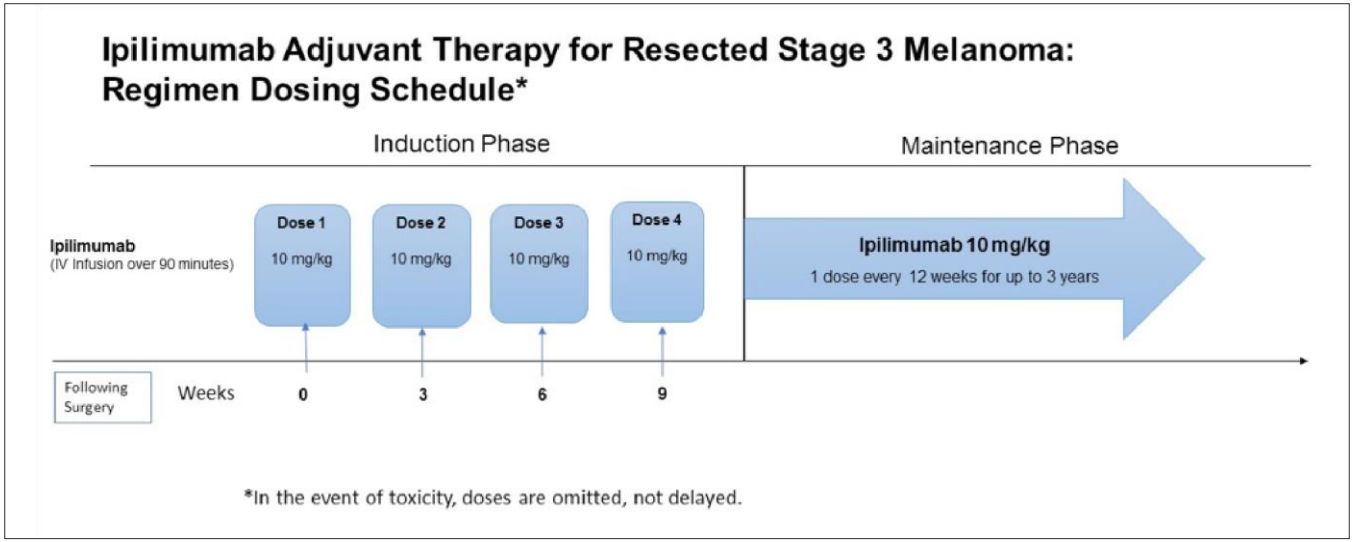

- Obtain pretreatment laboratory tests (eg, adrenal function [ACTH], clinical chemistries, liver function tests, and thyroid function tests) prior to initiation of therapy and before each cycle
- Ipilimumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if solution is cloudy, 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)

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

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.

AIM WITH IMMUNOTHERAPY FOUNDATION

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	• Serious condition requiring hospitalization/expert care, including supplemental oxygen, often mechanical ventilation, and fluid management
Anorexia	Decreased appetite	• 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	• 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	—	• 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	• 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	• 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	• 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*

AIM WITH IMMUNOTHERAPY FOUNDATION

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	• 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	• 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	• 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	• Encourage patient to report any eye symptoms immediately • Obtain ophthalmology referral • Anticipate standard dose ipilimumab holds/discontinuations*
Pyrexia	Elevated body temperature	• 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	• Anticipate does holds/discontinuations* • Intravenous fluids and corticosteroids (check creatine kinase levels)
Vision changes	Eye redness, pain, blurred vision, photophobia	• 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.

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;2:13461353.
- 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

PATIENT RESOURCES

ADDITIONAL INFORMATION RESOURCES

AIM at Melanoma Foundation (Ask an Expert program, patient symposia, drug resources, etc) https://www.aimatmelanoma.org/

American Cancer Society
https://www.cancer.org/

FINANCIAL ASSISTANCE

BMS RESOURCES
Financial assistance and personalized care coordination for patients.
http://www.bmsaccesssupport.bmscustomerconnect.com/cms__Main?name=patient
BMS Access Support 1-800-861-0048

Cancer Financial Aid Coalition
Facilitates communication, educates and advocates for patients.
www.cancerfac.org

Centers for Medicare and Medicaid Services (CMS)
Apply to determine if you are eligible for government assistance.
www.cms.gov or www.medicare.gov
800-633-4227

Lazarex Foundation
Provides assistance with travel costs for clinical trial participation. Ask your social work counselor for a referral if you have been consented to a clinical trial for melanoma.
www.lazarex.org

Needymeds
Database to search for free or low-cost medications, help with medical transportation and other resources.
www.needymeds.org

Patient Advocate Foundation
Provides assistance with mediation, financial stability, and other assistance. Funds subject to availability. Patient must meet their eligibility for financial assistance.
www.patientadvocate.org
800-532-5274

The Sam Fund for Young Adult Survivors of Cancer
Assists cancer survivors ages 21-39 with their transition into post-treatment life. This program distributes grants and scholarships in an effort to enable survivors to pursue goals.
www.thesamfund.org
info@thesamfund.org

PRESCRIPTION ASSISTANCE

CancerCare Co-Payment Assistance Foundation
Helps with the cost of medication. Availability of funds for patients with Stage IV melanoma subject to availability.
www.cancercarecopay.org
1-866-552-6729

Medicine Assistance Tool
Database to search for patient assistance resources offered by pharmaceutical companies.
www.medicineassistancetool.org/

Patient Advocate Foundation Co-Pay Relief
Provides direct financial support to patients who medically qualify. Availability of funds for patients with Stage IV melanoma subject to availability.
www.copays.org
1-866-512-3861

Good Days
Formerly known as the Chronic Disease Fund. Provides assistance with insurance co-pays, and prescription medications. Availability of funds for patients with Stage IV melanoma subject to availability.
www.mygooddays.org

HealthWell Foundation
For patients who cannot afford insurance premiums, co-payments, co-insurance, or other out-of-pocket health care costs. Availability of funds for patients with Stage IV melanoma subject to availability. Patient must also meet eligibility for financial assistance.
www.healthwellfoundation.org or
grants@healthwellfoundation.org
1-800-675-8416

The Assistance Fund, Inc
Provides prescription copay and financial assistance, including health insurance premiums. Availability of funds for patients with Stage IV melanoma subject to availability.
www.theassistancefund.org
1-855-845-3663

PAN Foundation
Provides financial assistance to cover out-of-pocket treatment costs. Availability of funds for patients with Stage IV melanoma subject to availability.
www.panfoundation.org
1-866-316-PANF (7263)

Patient Assistance Program
Comprehensive database of patient assistance programs offering free medications.
www.rxassist.org
info@rxassist.org

HOUSING

American Cancer Society – Hope Lodge
Provides free housing during treatment appointments. Requires a referral from your social worker.
www.cancer.org/
1-800-227-6333

TRANSPORTATION (AIR AND GROUND)

Medicaid
Ground transportation only. Sets up rides and provides mileage reimbursement for Medicaid patients only.
1-877-633-8747

Mercy Medical Angels
Provides free medical transportation (flights, gas cards, bus and train tickets) for patients with financial needs who need to travel more than 50 miles. Patients must meet their eligibility for financial assistance.
www.mercymedical.org/

Pilots for Patients
Provides free flights to people in need of medical treatment. Patient must be medically stable to fly and be ambulatory. Ask your social worker about a referral.
www.pilotsforpatients.org
318-322-5112