AIM WITH IMMUNOTHERAPY FOUNDATION | IMMUNO-ONCOLOGY ESSENTIALS

Nivolumab/Ipilimumab Combination Therapy for Melanoma

An HCP Tool From the Immuno-Oncology Essentials Initiative

Both nivolumab (Opdivo®) and ipilimumab (Yervoy®) are approved as monotherapies for the treatment of unresectable or metastatic (advanced) melanoma (discussed in separate nursing tools). They are also approved for use together as combination therapy in this patient population. Nivolumab and ipilimumab each improve anticancer responses and patient survival by inhibiting molecules known as checkpoints to enhance the patient's immune response to melanoma. Nivolumab inhibits the checkpoint known as programmed death receptor-1 (PD-1), and ipilimumab inhibits the checkpoint cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4).

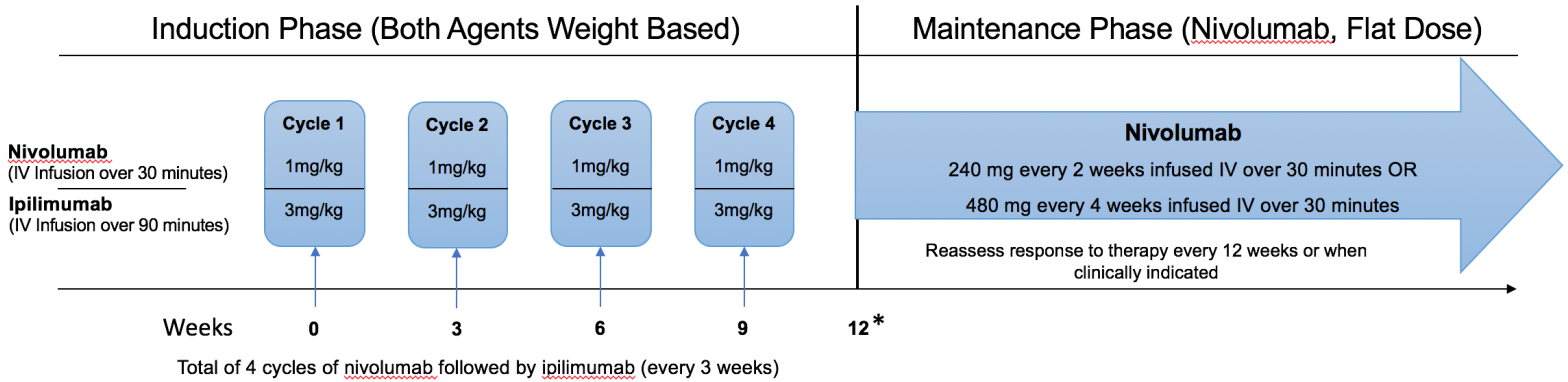
Antitumor activity is improved with nivolumab/ipilimumab combination therapy compared with either monotherapy, but the risk and severity of immune-related adverse events (irAEs) is also heightened.

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

DRUG DOSAGE/ADMINISTRATION

- 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
- Both nivolumab and ipilimumab are monoclonal antibodies administered via intravenous infusion, using separate intravenous lines
- Both nivolumab and ipilimumab are clear to opalescent, colorless to pale-yellow solutions. Their vials should be discarded if the solutions are cloudy, discolored, or contains extraneous particulate matter (other than a few translucent-to-white, proteinaceous particles)
- Neither ipilimumab nor nivolumab should be coadministered with each other or with other drugs through the same intravenous line
- When administered in combination with each other, nivolumab should be infused first, followed on the same day by ipilimumab, using separate infusion bags and in-line filters with pore sizes of 0.2 – 1.2 microns for each infusion
- Vials of nivolumab and ipilimumab should not be shaken
- The dosing schema for the induction and maintenance phases is shown below

Nivolumab + Ipilimumab Regimen Dosing Schedule



Total of 4 cycles of nivolumab followed by ipilimumab (every 3 weeks)

* Assess response.

SIDE EFFECTS AND THEIR MANAGEMENT

Because nivolumab and ipilimumab are immunotherapies that work by enhancing the patient's immune system, most adverse reactions associated with the combination are related to overactivity of the patient's immune system (ie, immune-related adverse events [irAEs]). Various organ systems or tissues may be affected. Risk and severity of irAEs are relatively higher when nivolumab and ipilimumab are coadministered than when used as monotherapies. The irAEs associated with nivolumab/ipilimumab combination therapy also tend to have an earlier onset.

- 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)
  - Nivolumab/ipilimumab may be held or discontinued depending on severity and/or persistence of the irAE
  - Referral to organ specialist should be considered
- irAEs associated with nivolumab/ipilimumab combination therapy can be categorized as 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 nivolumab/ipilimumab are shown in Appendix 2

Table 1. List of Care Step Pathways for the management of immune-related AEs associated with nivolumab/ipilimumab therapy

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
- Nivolumab/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 nivolumab/ipilimumab regimen with them at all times. This might be the nivolumab- and ipilimumab-specific wallet cards or at least emergency phone numbers and the side effects associated with the regimen. You may suggest they paperclip the wallet and insurance cards together so information about their regimen will be shared whenever they show the insurance card
- Advise patients to take pictures of any skin changes for documentation

QUESTIONS & ANSWERS

Q. After a well-tolerated induction with combination nivolumab/ipilimumab, a patient does well and has a significant response. The patient also does well on maintenance for a year, with stable disease, but then the disease begins to progress. Can the patient be reinduced with nivolumab/ipilimumab?

A. Reinduction can be a reasonable consideration. Evaluation for a clinical trial should always be taken into consideration when contemplating a change in therapy. Reintroduction with a single-agent immunotherapy is also an option.

Q. Should an asymptomatic endocrinopathy be treated?

A. A transient period of asymptomatic hyperthyroidism can sometimes be observed with PD-1 monotherapy, but it is more commonly observed early in treatment with combination nivolumab/ipilimumab. In the Checkmate 067 phase 3 trial, 15% of patients treated with the combination experienced hypothyroidism of any grade (Larkin J et al. *N Engl J Med*. 2015; 373:23-34).

This period is typically followed by hypothyroidism which can be clinically detectable and often requires permanent hormone replacement therapy.

Q. If it is not possible (because of side effects) for a highly motivated patient to complete all 4 induction cycles of combination nivolumab/ipilimumab, is it considered incomplete treatment or a "failure" to achieve a full course?

A. Goals of therapy are always geared toward safely adhering to the treatment plan regimen. Not all patients are able to complete all 4 induction infusions because of side effects. This is not deemed as a failure, as every patient responds to immune stimulation differently and not all patients can safely tolerate all 4 cycles.

Benefits have been observed with patients who did not complete all 4 induction cycles. In the phase 2 study, 68% of patients in a phase 2 trial who did not complete the induction regimen with nivolumab/ipilimumab had objective responses (Postow MA et al. *N Engl J Med*. 2015;372:2006-2017). These data show that it is possible to have a therapeutic immune response with fewer than 4 cycles of induction.

QUESTIONS & ANSWERS

Continued

Q. If patients do not finish all 4 doses of induction, can they go on to receive maintenance nivolumab?

A. This decision is made on an individual basis. Some safety factors taken into consideration are: (1) the severity of immune-related side effects; (2) the time it took for the side effects to resolve; and (3) the specific side effects that contributed to the truncation of induction. Oftentimes, patients have been able to successfully transition to maintenance nivolumab.

PATIENT RESOURCES

Financial Assistance

BMS Access Support
1 (800) 861-0048
http://www.bmsaccesssupport.bmscustomerconnect.com/patient

Additional Patient Resources

For more information about this therapy and support:

Guide to Opdivo/Yervoy Combination Treatment
https://www.opdivo.com/servlet/servlet.FileDownload?file=00Pi000000o0a9ZEAQ

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. 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.

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ADDITIONAL RESOURCES

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- Opdivo® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2018. Available at: http://packageinserts.bms.com/pi/pi_opdivo.pdf
- Opdivo patient alert card (wallet card) and other resources. http://www.opdivo.com/servlet/servlet.FileDownload?file=00P1Y00000v60IZUAY
- 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 nivolumab/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
Constipation/ abdominal pain (associated with nivolumab)	Infrequent stools/ difficulty stooling, abdominal pain	• Increase fluid, fiber; use caution with use of laxatives • Consider appropriate testing to evaluate bowel obstruction • Anticipate standard nivolumab dose holds/discontinuations* for Grade 3 and Grade 4 (constipation with manual evacuation indicated, severe abdominal pain, or life-threatening consequences)
Embryo-fetal toxicity	—	• Advise of risk to fetus and recommend use of effective contraception during treatment and for 3 months after ipilimumab and for 5 months after nivolumab is discontinued • Advise patient 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 • For ipilimumab: 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) • For nivolumab: Withhold nivolumab for new-onset moderate to severe neurologic symptoms; evaluate as described above; if other etiologies are ruled out, administer corticosteroids and permanently discontinue nivolumab for immune-mediated encephalitis

Management of other AEs associated with nivolumab/ipilimumab therapy.

(Continued)

Adverse event	Common symptoms	Common management/anticipatory guidance
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*
Infusion reaction	Chills/shaking, back pain, itching, flushing, difficulty breathing, hypotension, fever	• Nivolumab and/or ipilimumab: 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 nivolumab and/or ipilimumab; manage anaphylaxis via institutional protocol; monitor. Premedication with an antipyretic and antihistamine may be considered for future doses
Insomnia (associated with ipilimumab and corticosteroid therapy)	Difficulty falling or staying asleep	• Counsel patients on good sleep habits; prescription medications can be used if needed (should improve over time) • 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	• 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

Management of other AEs associated with nivolumab/ipilimumab therapy.

(Continued)

Adverse event	Common symptoms	Common management/anticipatory guidance
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)
Upper respiratory tract infection	Cough, runny nose, sore throat, nasal breathing	• Standard supportive care • Any cough needs to be evaluated for possible infection vs pneumonitis • Anticipate standard nivolumab treatment holds*

Dose holds/discontinuations

*For nivolumab: Withhold for any Grade 3 (severe) AE. Permanently discontinue for any Grade 4 (life-threatening) AE, persistent Grade 2-3 AE, any severe (Grade 3) AE that recurs, or when ≥10 mg/d prednisone or equivalent is required for 12 weeks. Resume treatment when AE returns to Grade 0 or 1.

For ipilimumab: Withhold for any Grade 2 (moderate) AE, and resume treatment when AE returns to Grade 0 or 1; permanently discontinue for any Grade 3-4 (life-threatening) AE, persistent Grade 2 AE lasting ≥6 weeks, or inability to reduce corticosteroid dose to 7.5 mg/d prednisone or equivalent.