

Nivolumab/Ipilimumab Combination Therapy

An HCP Tool From AIM with Immunotherapy

Both nivolumab (Opdivo[®]) and ipilimumab (Yervoy[®]) are approved as monotherapies for the treatment of many types of cancers. They are also approved for use together as combination therapy for the treatment of intermediate or poor risk advanced renal cell carcinoma, metastatic non-small cell lung cancer, metastatic or unresectable melanoma, unresectable advanced or metastatic esophageal squamous cell carcinoma, unresectable malignant pleural mesothelioma, hepatocellular carcinoma that was previously treated with sorafenib, and microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

Nivolumab and ipilimumab each improve anticancer responses and patient survival by inhibiting molecules known as checkpoints to enhance the patient's immune response. 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 patients receiving this combination of 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. Nivolumab should be administered first over 30 minutes, followed on the same day by ipilimumab administered over 30 minutes.
- 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 co-administered with each other or with other drugs through the same intravenous line
- When administered in combination, use 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
- When the drugs are used in combination for advanced renal cell carcinoma, hepatocellular carcinoma, or melanoma, Opdivo (30 minutes IV) and Yervoy (30 minutes IV) are usually given on the same day, every 3 weeks for a total of 4 doses or unacceptable toxicity if that occurs before 4 doses. After completing 4 combined doses, Opdivo is given alone every 2 or 4 weeks until disease progression or unacceptable toxicity.
- When the drugs are used in combination for microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan, Opdivo (30 minutes IV) and Yervoy (30 minutes IV) are usually given on the same day, every 3 weeks for a total of 4 doses or unacceptable toxicity if that occurs before 4 doses. After completing 4 combined doses, Opdivo is given alone every 2 or 4 weeks until disease progression or unacceptable toxicity.
- When the drugs are used in combination for metastatic or recurrent non-small cell lung cancer (NSCLC), whose tumors express PD-L1 (≥1%) as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations without chemotherapy, Opdivo is given every 2 weeks, whereas Yervoy is given every 6 weeks. If you are receiving the combination with chemotherapy, Opdivo is given every 3 weeks, while Yervoy is given every 6 weeks. The combination may be given until disease progression, unacceptable toxicity, or for up to 2 years in NSCLC.
- When the drugs are used in combination for advanced or metastatic esophageal squamous cell carcinoma, Opdivo is given as an IV for 30 minutes every two or three weeks, as indicated by your health care practitioner, in combination with Yervoy as an IV for 30 minutes every six weeks. The combination is continued until disease progression, unacceptable toxicity, or up to 2 years.
- When the drugs are used in combination for unresectable malignant pleural mesothelioma, Opdivo is given as an IV for 30 minutes every three weeks in combination with Yervoy given as an IV for 30 minutes every six weeks. The combination is continued until disease progression, unacceptable toxicity, or up to 2 years in patients without disease progression.



• The dosing schema below is for the induction and maintenance phases that would be administered for either melanoma, hepatocellular carcinoma, advanced renal cell carcinoma or previously treated, or metastatic dMMR/MSI-H colorectal patients.

Nivolumab + Ipilimumab Regimen Dosing Schedule



• The dosing schema are shown below is for non-small cell lung cancer. Clinical chemistries and liver function tests should be done before each cycle. Thyroid function tests should be done before Cycle 3 treatment, and every 6-12 weeks during nivolumab monotherapy.





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:

- o » Proactive assessment for early signs/symptoms of toxicity
- » Prompt intervention
- o » 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 immunerelated AEs associated with nivolumab/ipilimumab therapy

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	



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

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

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 $\geq 10 \text{ mg/d}$ 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.



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



- **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. This period is typically followed by hypothyroidism which can be clinically detectable and often requires permanent hormone replacement therapy.
- **Q.** What factors should be considered when selecting a combination regimen of nivolumab/ipilimumab with or without chemotherapy?
- A. Clinicians should consider the extent of disease burden, level of PD-L1 expression as well as underlying co-morbid medical conditions that may influence use of chemotherapeutic agents.

Q Does the side-effect profile differ with combination vs monotherapy immune checkpoint therapy and chemotherapy?

A. There are no new or unexpected side effects. However, clinicians will need to do a thorough assessment to differentiate the etiology of side effects to guide future treatments.

Q. How long will patients stay on nivolumab/ipilimumab?

A. The prescribing information indicates until disease progression or unacceptable toxicity or up to 24 months in patients without disease progression.



Q. Is PD-L1 testing required for patients to be eligible to receive nivolumab/ipilimumab?

A. For patients receiving nivolumab/ipilimumab alone. PD-L1 testing is required by an FDA-approved test. PD-L1 testing is reported as tumor proportion score (TPS). Low = <1%; Moderate = 1-49%; high = >50%. To be eligible for therapy, patients must have a TPS score ≥1%. For patients receiving nivolumab/ipilimumab plus chemotherapy, there is no PD-L1 requirement.

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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 should be discussed with the oncology team if a recommendation is being made for the patient to receive the injection series. Patients should be encouraged to get the inactivated influenza vaccine annually. The nasal spray flu vaccine is a live attenuated influenza vaccine and should not be administered to patients treated with immune checkpoint inhibitors.

Q. Does the safety profile of nivolumab/ipilimumab differ when it is used in various tumor types?

A. Generally, the safety profile of nivolumab/ipilimumab is similar across tumor types. However, the context may be different—patients with different tumor types may have differing comorbidities or underlying organ dysfunction. For example, lung cancer patients may have underlying lung disease that will exacerbate shortness of breath associated with pneumonitis.



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.

Q. What Child Pugh cirrhosis score is it safe to give nivolumab/ipilimumab?

A. Based on current safety data, only Child Pugh cirrhosis score A.

Q. Can patients with a history of or active hepatitis receive nivolumab/ipilimumab?

A. As long as a patient is not on active antiviral therapy and there is no hepatitis C co-infection, it is safe to administer nivolumab/ipilimumab with careful monitoring of liver function tests.

Q. Do patients have significant skin toxicities on nivolumab/ipilimumab as seen with sorafenib?

A. The skin toxicity seen most commonly with nivolumab/ipilimumab is an autoimmune mediated rash, which can become severe, but no hand-foot syndrome. Patients should perform routine skin self-examinations, and full body skin exams are recommended at each provider visit.

Q. Are patients more likely to experience diarrhea on nivolumab/ipilimumab if they had diarrhea on sorafenib?

A. No, but autoimmune mediated colitis is a common and serious potential side effect of nivolumab/ipilimumab. Patients should be carefully monitored for blood, mucus, and diarrhea.



Q. Is it safe to give nivolumab/ipilimumab in a patient with metastatic colorectal cancer to the liver with elevated liver function tests?

A. Yes, as long as the liver function tests are not greater than 3 times the upper limit of normal at baseline. However, immune mediated hepatitis is possible on nivolumab/ipilimumab, and patients should have careful and routine monitoring of liver function tests.

Q. How is diarrhea from nivolumab/ipilimumab different from that associated with other standard therapies such as 5-FU or irinotecan?

 A. Immune mediated colitis is a potentially serious toxicity of nivolumab/ipilimumab, presenting not only with diarrhea, but with blood and mucus, different than standard chemotherapy.
 Patients should be counseled to immediately report any new abdominal pain associated with blood, mucus and diarrhea to providers.

Q. Can nivolumab/ipilimumab cause or worsen peripheral neuropathy?

A. Immune mediated neuropathy is possible on nivolumab/ipilimumab, although this is a less commonly reported side effect. However, patients should remain observant to baseline neuropathy worsening with the use to nivolumab/ipilimumab.

Q. How are the skin toxicities such as rash different than rash seen with EGFR-inhibitors?

A. The immune mediated rash from nivolumab/ipilimumab is generally more puritic, erythematus, and distributed throughout the body without a pustular component, nor confined primarily to the face, scalp, and upper body, as seen with a EGFR-inhibitor-induced rash



ADDITIONAL RESOURCES

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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/

Bristol Myers Squibb

For more information about this therapy and support: Guide to Opdivo/Yervoy Combination Treatment www.opdivo.com/about-opdivo/how-the-combination-works-combinationtherapy

FINANCIAL ASSISTANCE

BMS Access Support

Financial assistance and personalized care coordination for patients 1-800-861-0048 www.bmsaccesssupport.bmscustomerconnect.com/cms_Main?name=patient

Cancer Financial Aid Coalition

Facilitates communication, educates and advocates for patients. <u>www.cancerfac.org</u>

Centers for Medicare and Medicaid Services (CMS)

Apply to determine if you are eligible for government assistance. <u>www.cms.gov</u> or <u>www.medicare.gov</u> 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. <u>www.needymeds.org</u>

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

PRESCRIPTION ASSISTANCE

CancerCare Co-Payment Assistance Foundation

Helps with the cost of medication. Availability of funds for patients subject to availability. <u>www.cancercarecopay.org</u> 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 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 subject to availability. <u>www.mygooddays.org</u>

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 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 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 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. <u>www.cancer.org/</u> 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