

Nivolumab/Relatlimab Combination Therapy

An HCP Tool from AIM with Immunotherapy

Opdualag™ is the brand name for the combination of nivolumab and relatlimab-rmbw. It is approved for the treatment of adult and pediatric patients 12 years of age or older (who weigh at least 40 kg or ~88 lbs) with unresectable or metastatic melanoma.

Note: The profile of nivolumab as a single-agent therapy is discussed in a separate document or HCP toolkit. However, relatlimab is *not* approved as a single-agent.

Nivolumab and relatlimab inhibit molecules known as immune checkpoints, which stop the immune system from overreacting to inflammation, but also from responding to the presence of a cancer cell. These agents are given to prevent the checkpoint, which enhances a patient's immune response to cancer and improves survival.

Nivolumab inhibits the checkpoint known as programmed death receptor-1 (PD-1), and relatlimab inhibits the checkpoint called lymphocyte activating gene 3 (LAG-3). The use of a combination approach that targets different parts of the immune system helps overcome drug resistance and improve outcomes. For this reason, nivolumab and relatlimab are given together as a single infusion.

However, while antitumor activity is improved with the combination, the risk and severity of immune-related adverse events (irAEs) are also heightened when compared with nivolumab alone.

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

- Ensure pretreatment laboratory tests have been obtained: CBC with differential, complete metabolic panel, and thyroid function tests including both TSH and free T4. Urine analysis is recommended
- Troponin and EKG should be considered
- Nivolumab and relatlimab are administered as a fixed drug combination and given as a single infusion
- Each vial contains 240 mg nivolumab and 80 mg relatlimab. Two vials are needed for the recommended dose of 480 mg nivolumab and 160 mg relatlimab
- Each vial contains a clear to opalescent, colorless to pale-yellow solution. Vials should be discarded if the solution is cloudy, discolored, or contains extraneous particulate matter (other than a few translucent-to-white, proteinaceous particles)
- Vial should not be shaken. Administer the fixed-dose combination of nivolumab/relatlimab over 30 minutes through an intravenous line with an in-line filter with pore sizes of 0.2 – 1.2 microns
- Do not co-administer other drugs through the same intravenous line
- The dosing schema is shown below.

Nivolumab and Relatlimab (Fixed-dose Combination) for Unresectable/Metastatic Melanoma: Regimen Schedule

Nivolumab and Relatlimab

480 mg nivolumab + 160 mg relatlimab (2 vials)
Single IV infusion over 30 minutes every 4 weeks

Continue until disease progression or unacceptable toxicity

SIDE EFFECTS AND THEIR MANAGEMENT

Because nivolumab and relatlimab 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. Although the side effect incidence is higher with the combination, the combination of nivolumab and relatlimab does not appear to cause any additional side effects or increase the occurrence of severe or life-threatening side effects when compared with nivolumab monotherapy

- 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/relatlimab 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/relatlimab combination therapy can be categorized as most common, less common but serious, and others that are easily overlooked
- Table 1 lists these irAEs

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

irAE category	Examples
Most common	Musculoskeletal pain Skin toxicities (pruritis, rash, etc) Gastrointestinal toxicity: Diarrhea and colitis Thyroiditis Hepatic toxicities
Less common but serious	Additional endocrinopathies <ul style="list-style-type: none"> • Hypophysitis (pituitary) • Adrenal insufficiency (adrenalitis) • Diabetes • Pneumonitis Myocarditis
Easily overlooked	Arthralgia/arthritis Mucositis/xerostomia Neuropathy Nephritis

Management of other AEs associated with nivolumab/relatlimab 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
Constipation/ abdominal pain (associated with nivolumab)	Infrequent stools/difficulty stooling, abdominal pain	<ul style="list-style-type: none"> • 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	—	<ul style="list-style-type: none"> • Advise of risk to fetus and recommend use of effective contraception during treatment and for at least 5 months after nivolumab/relatlimab is discontinued • Advise patient to tell HCP immediately if they or their partner suspect they are pregnant while taking therapy
Encephalitis	Headache, fever, nausea, tiredness, confusion, memory problems, sleepiness, hallucinations, seizures, stiff neck	<ul style="list-style-type: none"> • New-onset symptoms: hold nivo/rela, rule out infections or other causes; consult neurologist, obtain brain MRI and lumbar puncture • Patients with any grade encephalitis, anticipate high dose methylprednisolone (or equivalent), 1000 mg daily for 3-5 days. May also receive IVIG or plasma exchange (PLEX)
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 is increasing or 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 nivolumab/relatlimab therapy. (continued)

Adverse event	Common symptoms	Common management/anticipatory guidance
Infusion reaction	Chills/shaking, back pain, itching, rash, flushing, difficulty breathing, hypotension, fever, syncope or near syncope	<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: manage anaphylaxis via institutional protocol; monitor. Premedication with an antipyretic and/or antihistamine may be considered for future doses; allergy consult
Ocular: uveitis, conjunctivitis, blepharitis, episcleritis, iritis, optic neuritis, retinal detachment scleritis,	Red, painful, or dry eyes, blurry or double vision, eyelid swelling, photophobia, scotomas, difficulty moving the eyes.	<ul style="list-style-type: none"> • High grade ocular toxicity is rare • Most symptoms are mild and managed with topicals (artificial tears, corticosteroids, cycloplegic agents). Systemic steroids are rarely used • Consider referral to ophthalmology for any new ocular symptoms. Continue immunotherapy. Any visual compromise should prompt urgent referral, hold immunotherapy
Pyrexia	Elevated body temperature	<ul style="list-style-type: none"> • Transient low grade self-limiting fever can be managed conservatively. Persistent or recurrent fever requires work up to rule out infectious etiology and assess for irAE as fever can be present in a variety of irAEs (eg, colitis, bullous dermatoses, meningitis, hematologic) • Standard supportive care related to cytokine release • Anticipate standard dose holds/discontinuations*
Upper respiratory tract infection	Cough, runny nose, sore throat, nasal breathing	<ul style="list-style-type: none"> • Standard supportive care • Any new or worsening cough needs to be evaluated for possible infection vs pneumonitis • Anticipate standard nivolumab treatment holds*

Dose holds/discontinuations

In general, withhold nivolumab/relatlimab for severe (Grade 3) irAEs. Permanently discontinue for life-threatening (Grade 4) irAEs, recurrent severe (Grade 3) that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to <10 mg prednisone (or equivalent) per day within 12 weeks of initiating steroids.

*Exceptions to above recommendation include withholding nivolumab/relatlimab for the following Grade 2 irAEs: pneumonitis, colitis, neurologic toxicities, and nephritis with renal dysfunction. In addition, nivolumab/relatlimab should be withheld for ANY suspicion (regardless of grade) of myocarditis or exfoliative dermatologic condition.

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. UA should be considered to evaluate for baseline kidney disease. See individual irAE CSPs for more specific laboratory monitoring guidelines
- Baseline EKG and troponin are recommended for patients receiving combination therapy or patients at higher risk for myocarditis (cardiac comorbidities, DM)
- Nivolumab/relatlimab-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/relatlimab regimen with them at all times. This might be the [patient pocket guide for nivolumab-containing regimens](#) 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. Should an asymptomatic endocrinopathy be treated?

A. A transient period of asymptomatic hyperthyroidism can sometimes be observed with immune-checkpoint inhibitors (ICI), but it is more commonly observed early in treatment with combination nivolumab/relatlimab. This period is typically followed by hypothyroidism that can be clinically detectable and often requires permanent hormone replacement therapy. In the Relativity trial, 17% of patients treated with the combination experienced hypothyroidism of any grade.

Q. Are there standard dosage reductions for irAEs associated with nivolumab/relatlimab?

A. There are no dosage reductions for irAEs associated with nivolumab. The dose is either held until the irAE resolves sufficiently (typically to Grade 0 or Grade 1) or, if the irAE is severe enough, nivolumab is discontinued permanently.

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

A. The prescribing information indicates until disease progression or unacceptable toxicity. The interpretation of these criteria varies from institution to institution and from provider to provider.

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 Resource Section

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

FINANCIAL ASSISTANCE

BMS Access Support

1(800) 861-0048

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

For more information about this therapy and support:

Guide to Opdualag™ Combination Treatment

[Advanced Melanoma Treatment | Opdualag™ \(nivolumab and relatlimab-rmbw\)](#)

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 subject to availability.

www.cancercapecopay.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 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.

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 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 patients 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

ADDITIONAL RESOURCES

- Brahmer JR, Abu-Sbeih H, Ascierto PA, et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *J Immunother of Cancer*. 2021;9:e002435. doi:10.1136/jitc-2021-002435
- Opdualag™ [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; Revised 2022. Available at: https://packageinserts.bms.com/pi/pi_opdualag.pdf
- Opdualag™ patient pocket guide (wallet card). Bristol-Myers Squibb Company; 2022. Available at: <https://www.opdivohcp.com/assets/commercial/us/opdivo-hcp-pan-tumor/en/pdf/PatientPocketGuide.pdf>
- Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol*. 2021;39(36):4073-4126. doi:10.1200/JCO.21.01440
- Schneider BJ, Lacchetti C, Bollin K. Management of the top 10 most common immune-related adverse events in patients treated with immune checkpoint inhibitor therapy. *JCO Oncol Pract*. 2022;18(6):431-444. doi:10.1200/OP.21.00776
- Schoenfeld SR, Aronow ME, Leaf RK, Dougan M, Reynolds KL. Diagnosis and management of rare immune-related adverse events. *Oncologist*. 2020;25(1):6-14. doi:10.1634/theoncologist.2019-0083
- Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med*. 2022;386(1):24-34. doi:10.1056/NEJMoa2109970