

Nivolumab for MSI-H or dMMR Metastatic Colorectal Cancer (CRC)

An HCP Tool From the Immuno-Oncology Essentials Initiative

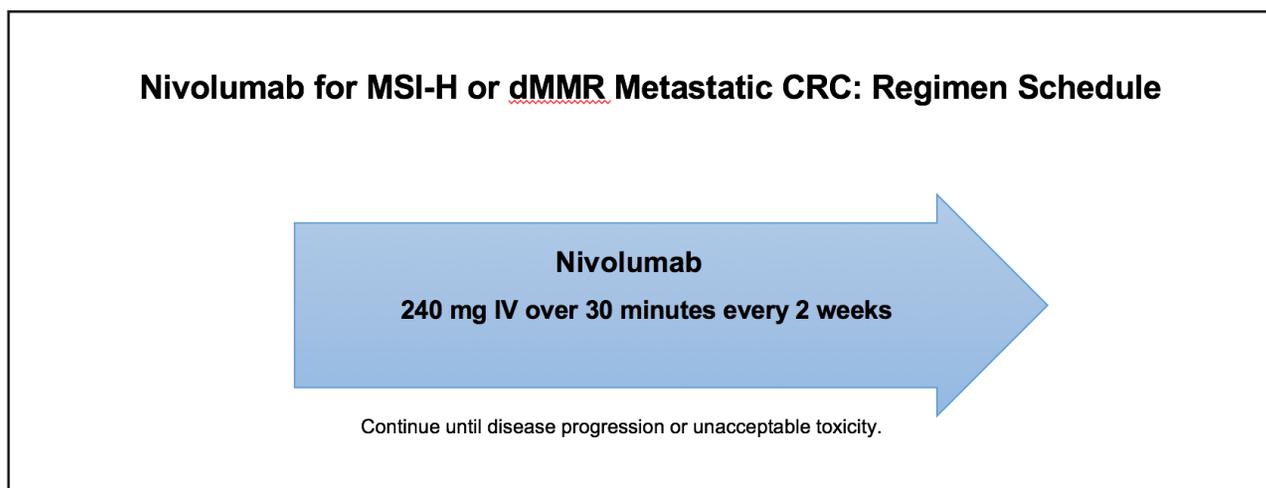
Approximately 5% or fewer of metastatic CRCs have defective DNA mismatch repair (dMMR) systems caused either by sporadic or genetic DNA mutations. Defective dMMR cause cellular hypermutations and high microsatellite instability (MSI-H), which make the cancer cells susceptible to immune checkpoint inhibitors. These cancers have recently been found in clinical trials to have significantly improved objective response rate and progression-free survival rates when patients are given nivolumab (Opdivo[®]), an anti-programmed death receptor (PD-1) monoclonal antibody checkpoint inhibitor.

Nivolumab is indicated as monotherapy for adult and pediatric (12 years and older) patients with MSI-H or dMMR metastatic CRC that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

This document is part of an overall HCP toolkit intended to assist providers in optimizing management of MSI-H or dMMR CRC in patients receiving newer GI cancer therapies.

DRUG DOSAGE/ADMINISTRATION

- For MSI-H or dMMR metastatic CRC, the recommended dosage of nivolumab (Opdivo®) is 240 mg administered as an intravenous infusion over 30 minutes every 2 weeks until disease progression or unacceptable toxicity



- Nivolumab is a clear to slightly opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter (other than a few translucent-to-white, proteinaceous particles)
- To prepare the dose, withdraw the required volume of nivolumab and transfer it into an intravenous container. This should be diluted with either 0.9% sodium chloride injection, USP, or 5% dextrose, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL
- Mix the diluted solution by gentle inversion. Do not shake
- Do not coadminister nivolumab with other drugs through the same intravenous line
- Nivolumab is classified as an irritant and may be safely administered via a central or peripheral line. It is important to ensure IV access before administration. Nivolumab should be administered through an intravenous line containing a sterile, non-pyrogenic, low-protein-binding in-line or add-on filter (pore size of 0.2-1.2 micrometers)

SIDE EFFECTS AND THEIR MANAGEMENT

Because nivolumab is an immunotherapy that works by enhancing the patient’s immune system, most adverse reactions associated with nivolumab 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 irAEs
 - » 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 (infliximab, mycophenolate mofetil, cyclophosphamide, etc) may be necessary
 - » Nivolumab will likely be held or discontinued depending on the severity and/or persistence of the irAE
 - » Referral to organ specialist should be considered, given that unique testing and management strategies may be required
- irAEs associated with nivolumab treatment can be categorized as 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 nivolumab are shown in Appendix 2

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

irAE category	Examples	Location
Most common	Skin toxicities (pruritus, rash, etc) Gastrointestinal toxicity: Diarrhea/colitis Thyroiditis Hepatic toxicities	Appendix 1
Less common but serious	Additional endocrinopathies <ul style="list-style-type: none"> - Hypophysitis (pituitary) - Adrenal insufficiency - Diabetes Pneumonitis	Appendix 1
Easily overlooked	Arthralgia/arthritis Mucositis/xerostomia 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. Please see the individual irAE CSPs for more detail about specific laboratory monitoring
- Nivolumab-related irAEs may occur at any time, including after treatment completion or discontinuation
- Unfortunately, currently, there is no way to predict the onset of irAEs and which patients will experience these events
- 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 HCPs and patients
- Unlike other irAEs, endocrinopathies usually do not resolve and may require lifelong hormone replacement therapy
- IrAEs have different time courses. New irAEs may become apparent upon tapering of corticosteroids used to treat an earlier onset irAE, since the new irAE can be suppressed or masked by immunosuppressive therapy. Therefore, during the taper period, patients should be advised to be on the lookout for early signs of new irAEs as well as recurrence of the original irAE that was being treated
- HCPs should encourage patients to carry information about their nivolumab regimen with them at all times. This might be the nivolumab-specific wallet card, or at least emergency phone numbers and a list of 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 the insurance card
- Advise patients to take pictures of any skin changes for documentation

QUESTIONS & ANSWERS

Q. How long will patients stay on nivolumab?

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.

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

A. There are no standard 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. I have experience using nivolumab for lung cancer. Is the safety profile different in those patients vs CRC patients?

A. Generally, the safety profile of nivolumab is similar across tumor types. However, the context may be different—patients with other 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, but metastatic colorectal cancer patients may have more problems with underlying diarrhea and/or colitis.

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) 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.

QUESTIONS & ANSWERS

Q: What are the differences between oxaliplatin-induced peripheral neuropathy (PN) and nerve problems seen with nivolumab?

A: Oxaliplatin PN tends to happen on the hands and feet with tingling and numbness. Nivolumab-induced nerve problems manifest as weakness and difficulty walking, but can also manifest with worsening numbness/tingling/functional impairment. It is imperative to ascertain baseline neurological deficits prior to initiating nivolumab for appropriate evaluation of worsening symptoms. For careful evaluation of worsening symptoms during therapy or after discontinuation accurate assessment of neuropathy may require patient demonstration (buttoning shirt, walking, testing grip).

Q: How do we test for MSI and MMR?

A: PCR for MSI and IHC for MMR can be requested to identify patients appropriate for treatment with nivolumab. Your pathologist may be able to perform the testing in your hospital/laboratory or may need to request testing from a reference lab.

Q: How is a nivolumab-induced rash different from an EGFR-induced rash seen with cetuximab or panitumumab?

A: Generally, an EGFR-induced rash manifests earlier, is more macular-papular, and less pruritic, and responsive to the STEPP skin protocol. A rash induced by nivolumab tends to be more pruritic, accompanied by a tightness/burning sensation, not acne-like, and generally responsive to oral corticosteroids.

PATIENT RESOURCES

Financial Assistance

BMS Access Support

1 (800) 861-0048

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

Additional Information Resources

Colorectal Cancer Alliance

<http://www.ccalliance.org/>

American Cancer Society Resource Section

<http://www.cancer.org/cancer/colon-rectal-cancer/treating/immunotherapy.html>

ADDITIONAL RESOURCES

- Boland CR, Goel A. Microsatellite instability in colorectal cancer. *Gastroenterology*. 2010;138:2073-2087.e3. doi: 10.1053/j.gastro.2009.12.064
- Boland PM, Ma WW. Immunotherapy for colorectal cancer. *Cancers*. 2017;9: E50. doi: 10.3390/cancers9050050
- 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.
- 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.
- Koopman M, Kortman GA, Mekenkamp L, et al. Deficient mismatch repair system in patients with sporadic advanced colorectal cancer. *Br J Cancer*. 2009;100:266-273.
- Kumar V, Chaudhary N, Garg M, Floudas CS, Soni P, Chandra AB. Current diagnosis and management of immune related adverse events (irAEs) induced by immune checkpoint inhibitor therapy. *Front Pharmacol*. 2017;8:49. doi: 10.3389/fphar.2017.00049
- McGettigan S, Rubin KM. Managing adverse events with PD-1 inhibitor therapy of advanced melanoma: consensus statements from the faculty of the Melanoma Nursing Initiative. *Clin J Oncol Nurs*. 2017;21(Suppl):42-51.
- Naidoo J, Page DB, Li BT, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint inhibitor antibodies. *Ann Oncol*. 2015;26:2375-2391.
- 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.

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ADDITIONAL RESOURCES

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- Nishijima TF, Shachar SS, Nyrop KA, Muss HB. Safety and tolerability of PD-1/PD-L1 inhibitors compared with chemotherapy in patients with advanced cancer: a meta-analysis. *Oncologist*. 2017;22:470-479.
- Opdivo Immune-Mediated Adverse Reactions Management Guide.
<http://www.opdivohcp.com/servlet/servlet.FileDownload?file=00Pi000000ijs1vEAA>
- Opdivo® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.
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=00Pi000000nywPmEAI>
- Overman MJ, McDermott R, Leach JL, et al. Nivolumab in patients with metastatic DNA mismatch repair-deficient or microsatellite instability-high colorectal cancer (CheckMate 142): an open-label, multicentre, phase 2 study. *Lancet Oncol*. 2017 Sep;18:1182-1191.
- Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017; 5: 95. doi: 10.1186/s40425-017-0300-z
- Spain L, Diem S, Larkin J. Management of toxicities of immune checkpoint inhibitors. *Cancer Treat Rev*. 2016;44:51-60.
- 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.
- Weber JS, Postow M, Lao CD, Schadendorf D. Management of adverse events following treatment with anti-programmed death-1 agents. *Oncologist*. 2016;21:1230-1240.

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 monotherapy.

Adverse event	Common symptoms	Common management/anticipatory guidance
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	Infrequent stools/ difficulty stooling, abdominal pain	<ul style="list-style-type: none"> • Consider other causes, such as opioid-induced constipation • Increase fluid, fiber; use laxatives with caution; suggest stool softeners and increased physical activity • Consider appropriate testing to evaluate bowel obstruction • Anticipate standard 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 patients to tell their HCPs immediately if they or their partners suspect they are pregnant while taking therapy • 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	<ul style="list-style-type: none"> • New-onset, moderate-to-severe symptoms: rule out infectious or other causes • Counsel neurologist, obtain brain MRI, and lumbar puncture • Anticipate standard dose-holds and discontinuations*
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; obtain MRI of brain with pituitary slices/pituitary protocol to confirm/rule out. • Anticipate standard dose holds/discontinuations*

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Management of other AEs associated with nivolumab monotherapy.

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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 nivolumab; 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) Anticipate standard dose holds/discontinuations*
Myocarditis	Shortness of breath; arrhythmia; light-headedness; chest pain; fatigue; nausea; edema	<ul style="list-style-type: none"> Obtain baseline ECG Assess cardiac biomarkers (BNP; troponin) Control cardiac diseases (and risk factors) optimally Consult cardiologists and consider corticosteroids if myocarditis is suspected Add additional immunosuppressive agents in severe, refractory cases Institute standard dose holds/discontinuations (in consultation with cardiologist)
Nausea/vomiting	Vomiting, queasiness, RUQ or LUQ pain	<ul style="list-style-type: none"> Rule out brain metastases and gastroenteritis 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*
Upper respiratory tract infection	Cough, runny nose, sore throat, nasal congestion	<ul style="list-style-type: none"> Evaluate potential causes—a dry cough and shortness of breath would increase concern for pneumonitis Standard supportive care Anticipate standard treatment holds*
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 nivolumab 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.