NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Nivolumab and relatlimab-rmbw (Opdualag™) Recommended as a **Preferred** Regimen for Treatment of Metastatic or Unresectable Cutaneous Melanoma

NCCN Guidelines – Melanoma: Cutaneous – Version 1.2023
Updated December 22, 2022

NCCN Category 1, Preferred Regimen	NCCN Guidelines® recommend nivolumab and relatlimab-rmbw (Opdualag™) as a **Category 1, preferred first-line treatment option** for metastatic or unresectable cutaneous melanoma
NCCN Category 2A, Preferred Regimen	NCCN Guidelines recommend nivolumab and relatlimab-rmbw (Opdualag™) as a **Category 2A, preferred second-line or subsequent therapy treatment option** for metastatic or unresectable cutaneous melanoma

Category 1: According to NCCN Categories of Evidence and Consensus, there is uniform NCCN consensus that the intervention is appropriate based upon high-level evidence.[1]

Category 2A: According to NCCN Categories of Evidence and Consensus, there is uniform NCCN consensus that the intervention is appropriate based upon lower-level evidence.[1]

Preferred regimen: According to NCCN Categories of Preference, interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.[1]

Please see updated NCCN Guidelines for a complete listing of all NCCN Guidelines recommended agents and other relevant information. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.[1]

NCCN=National Comprehensive Cancer Network® (NCCN®)

INDICATION

Opdualag is indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

Summary of Warnings and Precautions

Opdualag is associated with the following Warnings and Precautions: severe and fatal immune-mediated adverse reactions (IMARs) including pneumonitis, colitis, hepatitis, endocrinopathies, nephritis with renal dysfunction, dermatologic adverse reactions, myocarditis, and other immune-mediated adverse reactions; infusion-related reactions; complications of allogeneic hematopoietic stem cell transplantation (HSCT); and embryo-fetal toxicity.

Please see Important Safety Information for Opdualag throughout and U.S. Full Prescribing Information.

Opdualag
(nivolumab and relatlimab-rmbw)
Injection for intravenous use | 480 mg/160 mg

IMPORTANT SAFETY INFORMATION

Severe and Fatal Immune-Mediated Adverse Reactions

Immune-mediated adverse reactions (IMARs) listed herein may not include all possible severe and fatal immune-mediated adverse reactions.

IMARs which may be severe or fatal, can occur in any organ system or tissue. IMARs can occur at any time after starting treatment with a LAG-3 and PD-1/PD-L1 blocking antibodies. While IMARs usually manifest during treatment, they can also occur after discontinuation of Opdualag. Early identification and management of IMARs are essential to ensure safe use. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying IMARs. Evaluate clinical chemistries including liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment. In cases of suspected IMARs, initiate appropriate workup to exclude alternative etiologies, including infection. Institute medical management promptly, including specialty consultation as appropriate.

Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information). In general, if Opdualag requires interruption or discontinuation, administer systemic corticosteroid therapy (1 to 2 mg/kg/day prednisone or equivalent) until improvement to Grade 1 or less. Upon improvement to Grade 1 or less, initiate corticosteroid taper and continue to taper over at least 1 month. Consider administration of other systemic immunosuppressants in patients whose IMARs are not controlled with corticosteroid therapy. Toxicity management guidelines for adverse reactions that do not necessarily require systemic steroids (e.g., endocrinopathies and dermatologic reactions) are discussed below.

Immune-Mediated Pneumonitis

Opdualag can cause immune-mediated pneumonitis, which may be fatal. In patients treated with other PD-1/PD-L1 blocking antibodies, the incidence of pneumonitis is higher in patients who have received prior thoracic radiation. Immune-mediated pneumonitis occurred in 3.7% (13/355) of patients receiving Opdualag, including Grade 3 (0.6%), and Grade 2 (2.3%) adverse reactions. Pneumonitis led to permanent discontinuation of Opdualag in 0.8% and withholding of Opdualag in 1.4% of patients.

Immune-Mediated Colitis

Opdualag can cause immune-mediated colitis, defined as requiring use of corticosteroids and no clear alternate etiology. A common symptom included in the definition of colitis was diarrhea. Cytomegalovirus infection/reactivation has been reported in patients with corticosteroid-refractory immune-mediated colitis. In cases of corticosteroid-refractory colitis, consider repeating infectious workup to exclude alternative etiologies.

Immune-mediated diarrhea or colitis occurred in 7% (24/355) of patients receiving Opdualag, including Grade 3 (1.1%) and Grade 2 (4.5%) adverse reactions. Colitis led to permanent discontinuation of Opdualag in 2% and withholding of Opdualag in 2.8% of patients.

Immune-Mediated Hepatitis

Opdualag can cause immune-mediated hepatitis, defined as requiring the use of corticosteroids and no clear alternate etiology.

Immune-mediated hepatitis occurred in 6% (20/355) of patients receiving Opdualag, including Grade 4 (0.6%), Grade 3 (3.4%), and Grade 2 (1.4%) adverse reactions. Hepatitis led to permanent discontinuation of Opdualag in 1.7% and withholding of Opdualag in 2.3% of patients.

Immune-Mediated Endocrinopathies

Opdualag can cause primary or secondary adrenal insufficiency, hypophysitis, thyroid disorders, and Type 1 diabetes mellitus, which can be present with diabetic ketoacidosis. Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. In patients receiving Opdualag, adrenal insufficiency occurred in 4.2% (15/355) of patients receiving Opdualag, including Grade 3 (1.4%) and Grade 2 (2.5%) adverse reactions. Adrenal insufficiency led to permanent discontinuation of Opdualag in 1.1% and withholding of Opdualag in 0.8% of patients.

Hypophysitis can present with acute symptoms associated with mass effect such as headache, photophobia, or visual field defects. Hypophysitis can cause hypopituitarism; initiate hormone replacement as clinically indicated. Hypophysitis occurred in 2.5% (9/355) of patients receiving Opdualag, including Grade 3 (0.3%) and Grade 2 (1.4%) adverse reactions. Hypophysitis led to permanent discontinuation of Opdualag in 0.3% and withholding of Opdualag in 0.6% of patients.

Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism; initiate hormone replacement or medical management as clinically indicated. Thyroiditis occurred in 2.8% (10/355) of patients receiving

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IMPORTANT SAFETY INFORMATION (continued)

Immune-Mediated Endocrinopathies (continued)

Opdualag, including Grade 2 (1.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of Opdualag. Thyroiditis led to withholding of Opdualag in 0.3% of patients. Hyperthyroidism occurred in 6% (22/355) of patients receiving Opdualag, including Grade 2 (1.4%) adverse reactions. Hyperthyroidism did not lead to permanent discontinuation of Opdualag. Hyperthyroidism led to withholding of Opdualag in 0.3% of patients. Hypothyroidism occurred in 17% (59/355) of patients receiving Opdualag, including Grade 2 (11%) adverse reactions. Hypothyroidism led to the permanent discontinuation of Opdualag in 0.3% and withholding of Opdualag in 2.5% of patients.

Monitor patients for hyperglycemia or other signs and symptoms of diabetes; initiate treatment with insulin as clinically indicated. Diabetes occurred in 0.3% (1/355) of patients receiving Opdualag, a Grade 3 (0.3%) adverse reaction, and no cases of diabetic ketoacidosis. Diabetes did not lead to the permanent discontinuation or withholding of Opdualag in any patient.

Immune-Mediated Nephritis with Renal Dysfunction

Opdualag can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear etiology. In patients receiving Opdualag, immune-mediated nephritis and renal dysfunction occurred in 2% (7/355) of patients, including Grade 3 (1.1%) and Grade 2 (0.8%) adverse reactions. Immune-mediated nephritis and renal dysfunction led to permanent discontinuation of Opdualag in 0.8% and withholding of Opdualag in 0.6% of patients.

Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

Immune-Mediated Dermatologic Adverse Reactions

Opdualag can cause immune-mediated rash or dermatitis, defined as requiring use of steroids and no clear alternate etiology. Exfoliative dermatitis, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and Drug Rash with eosinophilia and systemic symptoms has occurred with PD-1/L-1 blocking antibodies. Topical emollients and/or topical corticosteroids may be adequate to treat mild to moderate non-exfoliative rashes.

Withhold or permanently discontinue Opdualag depending on severity (please see section 2 Dosage and Administration in the accompanying Full Prescribing Information).

Immune-mediated rash occurred in 9% (33/355) of patients, including Grade 3 (0.6%) and Grade 2 (3.4%) adverse reactions. Immune-mediated rash did not lead to permanent discontinuation of Opdualag. Immune-mediated rash led to withholding of Opdualag in 1.4% of patients.

Immune-Mediated Myocarditis

Opdualag can cause immune-mediated myocarditis, which is defined as requiring use of steroids and no clear alternate etiology. The diagnosis of immune-mediated myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, withhold dose, promptly initiate high dose steroids (prednisone or methylprednisolone 1 to 2 mg/kg/day) and promptly arrange cardiology consultation with diagnostic workup. If clinically confirmed, permanently discontinue Opdualag for Grade 2-4 myocarditis.

Myocarditis occurred in 1.7% (6/355) of patients receiving Opdualag, including Grade 3 (0.6%), and Grade 2 (1.1%) adverse reactions. Myocarditis led to permanent discontinuation of Opdualag in 1.7% of patients.

Other Immune-Mediated Adverse Reactions

The following clinically significant IMARs occurred at an incidence of <1% (unless otherwise noted) in patients who received Opdualag or were reported with the use of other PD-1/PD-L1 blocking antibodies. Severe or fatal cases have been reported for some of these adverse reactions: *Cardiac/Vascular:* pericarditis, vasculitis; *Nervous System:* meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis (including exacerbation), Guillain-Barré syndrome, nerve paresis, autoimmune neuropathy; *Ocular:* uveitis, iritis, and other ocular inflammatory toxicities can occur. Some cases can be associated with retinal detachment. Various grades of visual impairment, including blindness, can occur. If uveitis occurs in combination with other IMARs, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic steroids to reduce the risk of permanent vision loss; *Gastrointestinal*: pancreatitis including increases in serum amylase and lipase levels, gastritis, duodenitis; *Musculoskeletal and Connective Tissue:* myositis/polymyositis, rhabdomyolysis (and associated sequelae including renal failure), arthritis, polymyalgia rheumatica; *Endocrine*: hypoparathyroidism; *Other (Hematologic/Immune)*: hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, solid organ transplant rejection.

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IMPORTANT SAFETY INFORMATION (continued)

Infusion-Related Reactions

Opdualag can cause severe infusion-related reactions. Discontinue Opdualag in patients with severe or life-threatening infusion-related reactions. Interrupt or slow the rate of infusion in patients with mild to moderate infusion-related reactions. In patients who received Opdualag as a 60-minute intravenous infusion, infusion-related reactions occurred in 7% (23/355) of patients.

Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)

Fatal and other serious complications can occur in patients who receive allogeneic hematopoietic stem cell transplantation (HSCT) before or after being treated with a PD-1/PD-L1 receptor blocking antibody. Transplant-related complications include hyperacute graft-versus-host disease (GVHD), acute GVHD, chronic GVHD, hepatic veno-occlusive disease after reduced intensity conditioning, and steroid-requiring febrile syndrome (without an identified infectious cause). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and allogeneic HSCT.

Follow patients closely for evidence of transplant-related complications and intervene promptly. Consider the benefit versus risks of treatment with a PD-1/PD-L1 receptor blocking antibody prior to or after an allogeneic HSCT.

Embryo-Fetal Toxicity

Based on its mechanism of action and data from animal studies, Opdualag can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Opdualag and for at least 5 months after the last dose of Opdualag.

Lactation

There are no data on the presence of Opdualag in human milk, the effects on the breastfed child, or the effect on milk production. Because nivolumab and relatlimab may be excreted in human milk and because of the potential for serious adverse reactions in a breastfed child, advise patients not to breastfeed during treatment with Opdualag and for at least 5 months after the last dose.

Serious Adverse Reactions

In Relativity-047, fatal adverse reactions occurred in 3 (0.8%) patients who were treated with Opdualag; these included hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis. Serious adverse reactions occurred in 36% of patients treated with Opdualag. The most frequent serious adverse reactions reported in ≥1% of patients treated with Opdualag were adrenal insufficiency (1.4%), anemia (1.4%), colitis (1.4%), pneumonia (1.4%), acute myocardial infarction (1.1%), back pain (1.1%), diarrhea (1.1%), myocarditis (1.1%), and pneumonitis (1.1%).

Common Adverse Reactions and Laboratory Abnormalities

The most common adverse reactions reported in ≥20% of the patients treated with Opdualag were musculoskeletal pain (45%), fatigue (39%), rash (28%), pruritus (25%), and diarrhea (24%).

The most common laboratory abnormalities that occurred in ≥20% of patients treated with Opdualag were decreased hemoglobin (37%), decreased lymphocytes (32%), increased AST (30%), increased ALT (26%), and decreased sodium (24%).

Please see U.S. Full Prescribing Information for Opdualag.

REFERENCES:

1. Referenced with permission from The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Melanoma: Cutaneous Version 1.2023. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Accessed January 1, 2023. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
2. Opdualag [package insert]. Princeton, NJ: Bristol-Myers Squibb Company. 2023.

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