HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OPDUALAG safely and effectively. See full prescribing information for OPDUALAG.

OPDUALAG™ (nivolumab and relatlimab-rmbw) injection, for intravenous use
Initial U.S. Approval: 2022

----------RECENT MAJOR CHANGES----------

Warnings and Precautions (5.1) 3/2024

---------- INDICATIONS AND USAGE ----------

OPDUALAG is a combination of nivolumab, a programmed death receptor-1 (PD-1) blocking antibody, and relatlimab, a lymphocyte activation gene-3 (LAG-3) blocking antibody, indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma. (1)

---------- DOSAGE AND ADMINISTRATION ----------

- Adult patients and pediatric patients 12 years of age or older who weigh at least 40 kg: 480 mg nivolumab and 160 mg relatlimab intravenously every 4 weeks. (2)
- Administer OPDUALAG as an intravenous infusion over 30 minutes. (2)
- See full Prescribing Information for dosage modifications for adverse reactions (2.2) and preparation and administration instructions for the injection (2.3).

----------DOSAGE FORMS AND STRENGTHS ----------

- Injection: 240 mg of nivolumab and 80 mg of relatlimab per 20 mL (12 mg and 4 mg per mL) in a single-dose vial. (3)

----------CONTRAINDICATIONS----------

- None. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Immune-Mediated Adverse Reactions: (5.1)
  - Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue, including the following: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated dermatologic adverse reactions, immune-mediated nephritis with renal dysfunction, and immune-mediated myocarditis.
  - Monitor for early identification and management. Evaluate liver enzymes, creatinine, and thyroid function at baseline and periodically during treatment.
  - Withhold or permanently discontinue based on severity and type of reaction. (2.2)
- Infusion-related reactions: Interrupt, slow the rate of infusion, or permanently discontinue OPDUALAG (nivolumab and relatlimab-rmbw) based on severity of reaction. (2.2, 5.2)
- Complications of allogeneic HSCT: Fatal and other serious complications can occur in patient who receive allogeneic HSCT before or after being treated with a PD-1/PD-L1 blocking antibody. (5.3)
- Embryo-fetal toxicity: Can cause fetal harm. Advise females of reproductive potential of potential risk to a fetus and to use effective contraception. (5.4, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions (≥20%) are musculoskeletal pain, fatigue, rash, pruritus, and diarrhea. (6.1)

The most common laboratory abnormalities (≥20%) are decreased hemoglobin, decreased lymphocytes, increased AST, increased ALT, and decreased sodium. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- USE IN SPECIFIC POPULATIONS ----------

- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 3/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

1 INDICATIONS AND USAGE

OPDUALAG™ (nivolumab and relatlimab-rmbw) is indicated for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of OPDUALAG for adult patients and pediatric patients 12 years of age or older who weigh at least 40 kg is 480 mg nivolumab and 160 mg relatlimab administered intravenously every 4 weeks until disease progression or unacceptable toxicity occurs.

The recommended dosage for pediatric patients 12 years of age or older who weigh less than 40 kg has not been established *[see Use in Specific Populations (8.4)]*.

2.2 Dosage Modifications

No dose reduction for OPDUALAG is recommended. In general, withhold OPDUALAG for severe (Grade 3) immune-mediated adverse reactions (IMARs). Permanently discontinue OPDUALAG for life-threatening (Grade 4) IMARs, recurrent severe (Grade 3) IMARs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating steroids.

Dosage modifications for adverse reactions that require management different from these general guidelines are summarized in Table 1.

Table 1: Recommended Dosage Modifications for Adverse Reactions

Adverse Reaction	Severity*	Dose Modification
Immune-Mediated Adverse Reactions *[see Warnings and Precautions (5.1)]*		
Pneumonitis	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Colitis	Grade 2 or 3	Withhold[a]
	Grade 4	Permanently discontinue
Hepatitis	AST/ALT increases to more than 3 and up to 8 times ULN or Total bilirubin increases to more than 1.5 and up to 3 times ULN.	Withhold[a]
	AST or ALT increases to more than 8 times ULN regardless of baseline. or Total bilirubin increases to more than 3 times ULN.	Permanently discontinue
Endocrinopathies[b]	Grade 3 or 4	Withhold until clinically stable or permanently discontinue depending on severity
Nephritis with Renal Dysfunction	Grade 2 or 3 increased blood creatinine	Withhold[a]
	Grade 4 increased blood creatinine	Permanently discontinue
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold
	Confirmed SJS, TEN, or DRESS	Permanently discontinue
Myocarditis	Grade 2, 3, or 4	Permanently discontinue
Neurological Toxicities	Grade 2	Withhold[a]
	Grade 3 or 4	Permanently discontinue
Other Adverse Reactions		
Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*	Grade 1 or 2	Interrupt or slow the rate of infusion
	Grade 3 or 4	Permanently discontinue

* Based on National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

[a] Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper. Permanently discontinue if no complete or partial resolution within 12 weeks of last dose or inability to reduce prednisone to 10 mg per day (or equivalent) or less within 12 weeks of initiating steroids.

[b] Depending on clinical severity, consider withholding for Grade 2 endocrinopathy until symptom improvement with hormone replacement. Resume once acute symptoms have resolved.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, DRESS = Drug Rash with Eosinophilia and Systemic Symptoms, SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, ULN = upper limit normal

2.3 Preparation and Administration

OPDUALAG is a fixed-dose combination of nivolumab and relatlimab.

Visually inspect the solution in the drug product vial for particulate matter and discoloration prior to administration. OPDUALAG is a clear to opalescent, colorless to slightly yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white particles.

Preparation

- During preparation of the infusion solution, use aseptic technique to assure sterility, as the product does not contain a preservative.
- OPDUALAG can be administered diluted or undiluted and administered at a final concentration as specified in Table 2 below.
- Withdraw the required volume of OPDUALAG and transfer into an intravenous container. OPDUALAG is compatible with di(2-ethylhexyl)phthalate (DEHP)-plasticized polyvinyl chloride (PVC), ethyl vinyl acetate (EVA), and polyolefin (PO) intravenous bags.
- If diluting OPDUALAG prior to administration:
  - Dilute OPDUALAG solution with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion meeting the final concentration and maximum infusion volume parameters as specified in Table 2 below.
  - Then mix the diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials following infusion preparation.

Table 2: Maximum Infusion Volumes and Concentration Ranges by Patient Group

Patient Group	Maximum Infusion Volume (mL or mL/kg)	Concentration Range (mg/mL)*
Adult patients who weigh at least 40 kg and pediatric patients 12 years of age or older who weigh at least 40 kg	160 mL	Nivolumab: 3 mg/mL to 12 mg/mL Relatlimab: 1 mg/mL to 4 mg/mL
Adult patients who weigh less than 40 kg	4 mL/kg	Nivolumab: 3 mg/mL to 12 mg/mL Relatlimab: 1 mg/mL to 4 mg/mL

* The concentration range in each group includes 12 mg/mL nivolumab and 4 mg/mL relatlimab as the upper limit, which represents a scenario in which the drug product is infused without dilution.

Storage of Prepared Solution

Store the prepared solution either:

- at room temperature and room light for no more than 8 hours from the time of preparation to the end of the infusion. Discard the prepared solution if not used within 8 hours from the time of preparation;

-or-

under refrigeration at 2°C to 8°C (36°F to 46°F) with protection from light for no more than 24 hours from the time of preparation, which includes the time allowed for equilibration of the infusion bag to room temperature and the duration of the infusion. Discard the prepared solution if not used within 24 hours from the time of preparation.

Do not freeze.

Administration

- Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line polyethersulfone (PES), nylon, or polyvinylidene fluoride (PVDF) filter (pore size of 0.2 micrometer to 1.2 micrometer).
- Flush the intravenous line at the end of the infusion.
- Do not coadminister other drugs through the same intravenous line.

3 DOSAGE FORMS AND STRENGTHS

Injection: 240 mg nivolumab and 80 mg relatlimab per 20 mL (12 mg and 4 mg per mL) as a clear to opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Severe and Fatal Immune-Mediated Adverse Reactions

OPDUALAG potentially breaks peripheral tolerance and induces immune-mediated adverse reactions (IMARs) *[see Clinical Pharmacology (12.1)]*. Important IMARs listed under Warnings and Precautions may not include all possible severe and fatal IMARs.

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, IMARs can also manifest after discontinuation.

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 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 *[see Dosage and Administration (2.2)]*. 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.

Systemic corticosteroids were required in 100% (13/13) of patients with pneumonitis. Pneumonitis resolved in 85% of the 13 patients. Of the 5 patients in whom OPDUALAG was withheld for pneumonitis, 5 reinitiated OPDUALAG after symptom improvement; of these, none had recurrence of pneumonitis.

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.

Systemic corticosteroids were required in 100% (24/24) of patients with diarrhea or colitis. Colitis resolved in 83% of the 24 patients. Of the 10 patients in whom OPDUALAG was withheld for colitis, 9 reinitiated OPDUALAG after symptom improvement; of these, 67% had recurrence of colitis.

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.

Systemic corticosteroids were required in 100% (20/20) of patients with hepatitis. Hepatitis resolved in 70% of the 20 patients. Of the 8 patients in whom OPDUALAG was withheld for hepatitis, 6 reinitiated OPDUALAG after symptom improvement; of these, 50% had recurrence of hepatitis.

Immune-Mediated Endocrinopathies

Adrenal Insufficiency

OPDUALAG can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. Withhold OPDUALAG depending on severity *[see Dosage and Administration (2.2)]*.

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.

Approximately 87% (13/15) of patients with adrenal insufficiency received hormone replacement therapy. Systemic corticosteroids were required in 87% (13/15) of patients with adrenal insufficiency. Adrenal insufficiency resolved in 33% of the 15 patients. Of the 3 patients in whom OPDUALAG was withheld for adrenal insufficiency, all 3 reinitiated OPDUALAG after symptom improvement.

OPDUALAG™ (nivolumab and relatlimab-rmbw)

Hypophysitis

OPDUALAG can cause immune-mediated hypophysitis. 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. Withhold or permanently discontinue OPDUALAG depending on severity *[see Dosage and Administration (2.2)]*.

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.

All (9/9) of patients with hypophysitis received hormone replacement therapy. Systemic corticosteroids were required in 100% (9/9) of patients with hypophysitis. Hypophysitis resolved in 22% of the 9 patients. Of the 2 patients in whom OPDUALAG was withheld for hypophysitis, none reinitiated OPDUALAG after symptom improvement.

Thyroid Disorders

OPDUALAG can cause immune-mediated thyroid disorders. Thyroiditis can present with or without endocrinopathy. Hypothyroidism can follow hyperthyroidism. Initiate hormone replacement or medical management as clinically indicated. Withhold or permanently discontinue OPDUALAG depending on severity *[see Dosage and Administration (2.2)]*.

Thyroiditis

Thyroiditis occurred in 2.8% (10/355) of patients receiving OPDUALAG, including Grade 2 (1.1%) adverse reactions. Thyroiditis did not lead to permanent discontinuation of OPDUALAG. Thyroiditis led withholding of OPDUALAG in 0.3% of patients.

Systemic corticosteroids were required in 20% (2/10) of patients with thyroiditis. Thyroiditis resolved in 90% of the 10 patients. For the 1 patient in whom OPDUALAG was withheld for thyroiditis, OPDUALAG was reinitiated after symptom improvement without recurrence of thyroiditis.

Hyperthyroidism

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.

Systemic corticosteroids were required in 23% (5/22) of patients. Hyperthyroidism resolved in 82% of the 22 patients. For the 1 patient in whom OPDUALAG was withheld for hyperthyroidism, OPDUALAG was reinitiated after symptom improvement without recurrence of hyperthyroidism.

Hypothyroidism

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.

None of the patients with hypothyroidism required systemic corticosteroids. Hypothyroidism resolved in 12% of the 59 patients. Of the 9 patients in whom OPDUALAG was withheld for hypothyroidism, 6 reinitiated OPDUALAG after symptom improvement; of these, 33% had recurrence of hypothyroidism.

Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis

Monitor patients for hyperglycemia or other signs and symptoms of diabetes. Initiate treatment with insulin as clinically indicated. Withhold or permanently discontinue OPDUALAG depending on severity *[see Dosage and Administration (2.2)]*.

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 alternate etiology. Withhold or permanently discontinue OPDUALAG depending on severity *[see Dosage and Administration (2.2)]*.

Immune-mediated nephritis and renal dysfunction occurred in 2% (7/355) of patients receiving OPDUALAG, 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.

Systemic corticosteroids were required in 100% (7/7) of patients with nephritis and renal dysfunction. Nephritis and renal dysfunction resolved in 71% of the 7 patients. Of the 2 patients in whom OPDUALAG was withheld for nephritis or renal dysfunction, 1 reinitiated OPDUALAG after symptom improvement without recurrence of nephritis or renal dysfunction.

OPDUALAG™ (nivolumab and relatlimab-rmbw)

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 *[see Dosage and Administration (2.2)]*.

Immune-mediated rash occurred in 9% (33/355) of patients receiving OPDUALAG, 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.

Systemic corticosteroids were required in 88% (29/33) of patients with immune-mediated rash. Rash resolved in 70% of the 33 patients. Of the 5 patients in whom OPDUALAG was withheld for immune-mediated rash, 4 reinitiated OPDUALAG after symptom improvement; of these, 25% had recurrence of immune-mediated rash.

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 *[see Dosage and Administration (2.2)]*.

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.

Systemic corticosteroids were required in 100% (6/6) of patients with myocarditis. Myocarditis resolved in 100% of the 6 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, other transplant (including corneal graft) rejection.

5.2 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 or moderate infusion-related reactions *[see Dosage and Administration (2.2)]*.

In patients who received OPDUALAG as a 60-minute intravenous infusion, infusion-related reactions occurred in 7% (23/355) of patients.

5.3 Complications of Allogeneic Hematopoietic Stem Cell Transplantation

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) *[see Adverse Reactions (6.1)]*. 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.

5.4 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. In animal reproduction studies, administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with OPDUALAG for at least 5 months after the last dose of OPDUALAG *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling.

- Severe and Fatal IMARs *[see Warnings and Precautions (5.1)]*
- Infusion-Related Reactions *[see Warnings and Precautions (5.2)]*
- Complications of Allogeneic HSCT *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of OPDUALAG was evaluated in RELATIVITY-047, a randomized (1:1), double-blinded trial in 714 patients with previously untreated metastatic or unresectable melanoma *[see Clinical Studies (14)]*. Patients received intravenous OPDUALAG (nivolumab 480 mg and relatlimab 160 mg) every 4 weeks (n=355) or nivolumab 480 mg by intravenous infusion every 4 weeks (n=359). Patients were treated with OPDUALAG or nivolumab until disease progression or unacceptable toxicity. The median duration of exposure was 6 months (range: 0 to 31 months) in OPDUALAG-treated patients and 5 months (range: 0 to 32 months) in nivolumab-treated patients.

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%). Fatal adverse reaction occurred in 3 (0.8%) patients who were treated with OPDUALAG; these included hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis.

OPDUALAG was permanently discontinued due to adverse reactions in 18% of patients. Adverse reactions which resulted in permanent discontinuation of OPDUALAG in ≥1% of patients included myocarditis (1.7%) and pneumonitis (1.4%).

Dosage interruptions due to an adverse reaction occurred in 43% of patients who received OPDUALAG. Adverse reactions that required dosage interruption in ≥2% of patients who received OPDUALAG were diarrhea (3.9%), troponin increased (3.9%), AST increased (2.8%), troponin T increased (2.8%), ALT increased (2.3%), arthralgia (2.3%), hypothyroidism (2.3%), anemia (2%), fatigue (2%), pneumonitis (2%), and rash (2%).

The most common (≥20%) adverse reactions that occurred in patients treated with OPDUALAG were musculoskeletal pain (45%), fatigue (39%), rash (28%), pruritus (25%), and diarrhea (24%). The most common (≥20%) laboratory abnormalities that occurred in patients treated with OPDUALAG were decreased hemoglobin (37%), decreased lymphocytes (32%), increased AST (30%), increased ALT (26%), and decreased sodium (24%).

Tables 3 and 4 summarize both the adverse reactions and laboratory abnormalities, respectively, in RELATIVITY-047.

Table 3: Adverse Reactions in ≥15% of Patients - RELATIVITY-047

Adverse Reaction	OPDUALAG (n=355)		Nivolumab (n=359)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Musculoskeletal and Connective Tissue				
Musculoskeletal pain[a]	45	4.2	31	1.7
General				
Fatigue[a]	39	2	29	0.6
Skin and Subcutaneous Tissue				
Rash[a]	28	1.4	21	1.9
Pruritus	25	0	17	0.6
Gastrointestinal				
Diarrhea[a]	24	2	17	1.4
Nausea	17	0.6	14	0
Nervous System				
Headache[a]	18	0.3	12	0.3
Endocrine				
Hypothyroidism[a]	17	0	14	0
Metabolism and Nutrition Disorders				
Decreased appetite	15	0.6	7	0.3
Respiratory, Thoracic and Mediastinal Disorders				
Cough[a]	15	0.3	11	0

Toxicity was graded per NCI CTCAE v5.
[a] Includes multiple terms.

Clinically relevant adverse reactions in <15% of patients who received OPDUALAG included vitiligo, adrenal insufficiency, myocarditis, and hepatitis.

Table 4: Laboratory Abnormalities (≥15%) That Worsened from Baseline[a] in Patients Who Received OPDUALAG in RELATIVITY-047

Laboratory Abnormality	OPDUALAG[a]		Nivolumab[a]	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Chemistry				
Increased AST	30	2.3	22	1.4
Increased ALT	26	3.2	25	2
Decreased sodium	24	1.2	21	0.6
Increased alkaline phosphatase	19	0.6	17	0.9
Increased creatinine	19	0	16	0
Hematology				
Decreased hemoglobin	37	2.7	31	3.5
Decreased lymphocytes	32	2.5	24	2.9

[a] Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available: OPDUALAG group (range: 280 to 342 patients) and nivolumab group (range: 276 to 345 patients).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animals and mechanism of action, OPDUALAG can cause fetal harm when administered to a pregnant woman. Administration of nivolumab to cynomolgus monkeys from the onset of organogenesis through delivery resulted in increased abortion and premature infant death *(see Data)*. Human IgG4 is known to cross the placenta; therefore, nivolumab and relatlimab have the potential to be transmitted from the mother to the developing fetus. The effects of OPDUALAG are likely to be greater during the second and third trimesters of pregnancy. There are no available data on OPDUALAG in pregnant women to evaluate a drug-associated risk. Advise the patient of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

OPDUALAG™ (nivolumab and relatlimab-rmbw)

Data

Animal Data

OPDUALAG injection for intravenous use contains nivolumab and relatlimab *[see Description (11)]*.

Nivolumab:

One function of the PD-1/PD-L1 pathway is to preserve pregnancy by maintaining immune tolerance to the fetus. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis through delivery, at exposure levels of between 9 and 42 times higher than those observed at the clinical dose of 3 mg/kg (based on AUC). Nivolumab administration resulted in a non-dose-related increase in spontaneous abortion and increased neonatal death. In surviving infants (18 of 32 compared to 11 of 16 vehicle-exposed infants) of cynomolgus monkeys treated with nivolumab, there were no apparent malformations and no effects on neurobehavioral, immunological, or clinical pathology parameters throughout the 6-month postnatal period.

Relatlimab:

There are no available animal data on relatlimab. The effects of a murine surrogate anti-LAG-3 antibody was evaluated in mice using syngeneic and allogeneic breeding models. When anti-LAG-3 antibodies were administered beginning on gestation day 6, there were no maternal or developmental effects in either syngeneic or allogeneic breedings.

8.2 Lactation

Risk Summary

There are no data on the presence of nivolumab and relatlimab in human milk, the effects on the breastfed child, or the effects 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 *[see Pharmacokinetics (12.3)]*.

8.3 Females and Males of Reproductive Potential

OPDUALAG can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to initiating OPDUALAG *[see Use in Specific Populations (8.1)]*.

Contraception

Advise females of reproductive potential to use effective contraception during treatment and for at least 5 months following the last dose of OPDUALAG *[see Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

The safety and effectiveness of OPDUALAG for the treatment of unresectable or metastatic melanoma have been established in pediatric patients 12 years of age or older who weigh at least 40 kg. Use of OPDUALAG for this indication is supported by evidence from an adequate and well-controlled study in adults and additional data analyses that suggest that nivolumab and relatlimab exposures in pediatric patients 12 years of age who weigh at least 40 kg are expected to result in similar safety and efficacy to that of adults. The pharmacokinetics of monoclonal antibodies and the course of unresectable or metastatic melanoma are sufficiently similar in adults and pediatric patients 12 years of age or older to allow extrapolation of data from adult patients to pediatric patients 12 years of age or older (who weigh at least 40 kg). A recommended dosage for pediatric patients 12 years of age or older who weigh less than 40 kg has not been established *[see Adverse Reactions (6.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

The safety and effectiveness of OPDUALAG have not been established in pediatric patients 12 years of age or older who weigh less than 40 kg, and pediatric patients younger than 12 years of age.

8.5 Geriatric Use

Of the 355 patients treated with OPDUALAG in RELATIVITY-047, 47% of patients were 65 years or older, 29% were 65 to 74 years, 17% were 75 to 84 years, and 1.7% were 85 years and older. No overall differences in safety or effectiveness were observed between elderly patients and younger patients.

11 DESCRIPTION

Nivolumab and relatlimab-rmbw is a fixed-dose combination of two IgG4 kappa monoclonal antibodies (mAbs). Nivolumab is a programmed death receptor-1 (PD-1) blocking antibody that has a calculated molecular mass of 146 kDa and is expressed in a recombinant Chinese Hamster Ovary (CHO) cell line. Relatlimab is a lymphocyte activation gene-3 (LAG-3) blocking antibody that has a calculated molecular mass of 148 kDa and is expressed in a recombinant CHO cell line.

OPDUALAG (nivolumab and relatlimab-rmbw) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution that may contain few translucent-to-white particles. OPDUALAG is supplied as 240 mg of nivolumab and 80 mg of relatlimab in a 20 mL single-dose vial for intravenous use. Each mL of OPDUALAG solution contains

OPDUALAG™ (nivolumab and relatlimab-rmbw)

12 mg of nivolumab, 4 mg of relatlimab, and histidine (1.1 mg), L-histidine hydrochloride monohydrate (2.7 mg), pentetic acid (0.008 mg), polysorbate 80 (0.5 mg), sucrose (85.6 mg), and Water for Injection, USP. The pH is 5.8.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Relatlimab is a human IgG4 monoclonal antibody that binds to the LAG-3 receptor, blocks interaction with its ligands, including MHC II, and reduces LAG-3 pathway-mediated inhibition of the immune response. Antagonism of this pathway promotes T cell proliferation and cytokine secretion.

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2, and reduces PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

The combination of nivolumab (anti-PD-1) and relatlimab (anti-LAG-3) results in increased T-cell activation compared to the activity of either antibody alone. In murine syngeneic tumor models, LAG-3 blockade potentiates the anti-tumor activity of PD-1 blockage, inhibiting tumor growth and promoting tumor regression.

12.2 Pharmacodynamics

The exposure-response relationship and time course of pharmacodynamic response for the safety and effectiveness of OPDUALAG have not been fully characterized.

12.3 Pharmacokinetics

The pharmacokinetics (PK) of relatlimab following the administration of OPDUALAG were characterized in patients with cancer who received relatlimab 20 to 800 mg every 2 weeks (0.25 to 10 times the approved recommended dosage) or 160 to 1440 mg every 4 weeks (1 to 9 times the approved recommended dosage) either as a monotherapy or in combination with nivolumab dosages of 80 or 240 mg every 2 weeks or 480 mg every 4 weeks.

Steady-state concentrations of relatlimab were reached by 16 weeks with an every 4-week regimen and the systemic accumulation was 1.9-fold. The average concentration (C_{avg}) of relatlimab after the first dose increased dose proportionally at doses ≥160 mg every 4 weeks.

Following the recommended dosage, the geometric mean [coefficient of variation (CV%)] maximum and average concentrations (C_{max} and C_{avg}) of relatlimab at steady state were 62.2 (30%), and 28.8 (45%) µg/mL, respectively; and the mean C_{max} and C_{avg} of nivolumab at steady state were 187 (33%) and 94.4 (43%) µg/mL, respectively.

In RELATIVITY-047, the nivolumab geometric mean minimum concentration (C_{min}) at steady state in the OPDUALAG arm was comparable to the nivolumab arm.

Distribution

The geometric mean (CV%) volume of distribution at steady state of relatlimab is 6.6 L (20%) and 6.6 L (19%) of nivolumab.

Elimination

The geometric mean (CV%) clearance of relatlimab is 5.5 mL/h (41%) at steady state, 10% lower than after the first dose [6 mL/h (39%)]. Following OPDUALAG (nivolumab 480 mg and relatlimab 160 mg administered every 4 weeks) administration, the geometric mean (CV%) effective half-life ($t_{1/2}$) of relatlimab is 26.2 days (37%).

The geometric mean (CV%) clearance of nivolumab is 7.6 mL/h (40%) at steady state, 21% lower than after the first dose [9.6 mL/h (40%)] and the terminal $t_{1/2}$ is 26.5 days (36%).

Specific Populations

The following factors had no clinically important effect on the clearance of nivolumab and relatlimab: age (17 to 92 years), sex, race (White, Asian, and Black/African American), mild or moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2), mild hepatic impairment (total bilirubin [TB] less than or equal to upper limit of normal [ULN] and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST). The effects of severe renal impairment, or severe hepatic impairment on the pharmacokinetics of nivolumab and relatlimab are unknown.

Pediatric patients:

The exposures of nivolumab and relatlimab in pediatric patients 12 years of age or older who weigh at least 40 kg are expected to be in the range of exposures in adult patients at the recommended dosage.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including studies of nivolumab and relatlimab-rmbw products, or nivolumab products.

During the initial 24-month treatment period in RELATIVITY-047, the incidence of:

- anti-nivolumab antibodies and neutralizing antibodies in the OPDUALAG group was 3.8% (11/288) and 0.3% (1/288), respectively, which was similar to that observed in the nivolumab group: 5.9% (16/272) and 0.4% (1/272), respectively.
- anti-relatlimab antibodies and neutralizing antibodies in the OPDUALAG group was 5.6% (16/286) and 0.3% (1/286), respectively.

Because of the low incidence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, or effectiveness of OPDUALAG is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

OPDUALAG contains nivolumab and relatlimab.

No studies have been performed to assess the potential of nivolumab or relatlimab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab or relatlimab.

13.2 Animal Toxicology and/or Pharmacology

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. *Mycobacterium tuberculosis*–infected PD-1 knockout mice exhibited markedly decreased survival compared with wild-type controls, which correlated with increased bacterial proliferation and inflammatory responses in these animals. PD-1 blockade using a primate anti-PD-1 antibody was also shown to exacerbate *M. tuberculosis* infection in rhesus macaques. PD-1 and PD-L1 knockout mice receiving PD-L1 blocking antibody have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

Inhibition of PD-1 and LAG-3 results in autoimmunity in preclinical models. Mice deficient in both PD-1 and LAG-3 develop lethal systemic autoimmunity that includes myocarditis.

In a 1-month study in monkeys dosed with nivolumab and relatlimab, inflammation within the central nervous system (choroid plexus, vasculature, meninges, spinal cord) and the reproductive tract (epididymis, seminal vesicles, and testes) was observed.

14 CLINICAL STUDIES

The efficacy of OPDUALAG was investigated in RELATIVITY-047 (NCT03470922), a randomized (1:1), double-blinded trial in 714 patients with previously untreated metastatic or unresectable Stage III or IV melanoma. Patients were allowed to have received prior adjuvant or neoadjuvant melanoma therapy: anti-PD-1, anti-CTLA-4, or BRAF-MEK inhibitors were allowed if received at least 6 months between the last dose of therapy and date of recurrence; interferon therapy was allowed if the last dose was at least 6 weeks prior to randomization. The trial excluded patients with active autoimmune disease, medical conditions requiring systemic treatment with moderate or high dose corticosteroids or immunosuppressive medications, uveal melanoma, and active or untreated brain or leptomeningeal metastases. Patients were randomized to receive OPDUALAG (nivolumab 480 mg and relatlimab 160 mg) by intravenous infusion every 4 weeks (n=355) or nivolumab 480 mg by intravenous infusion every 4 weeks (n=359) until disease progression or unacceptable toxicity. Randomization was stratified by tumor PD-L1 expression (≥1% vs. <1%) using PD-L1 IHC 28-8 pharmDx test, LAG-3 expression (≥1% vs. <1%) using a clinical trial assay, BRAF V600 mutation status (V600 mutation positive vs. wild type), and M stage per the American Joint Committee on Cancer (AJCC) version 8 staging system (M0/M1any[0] vs. M1any[1]).

The major efficacy outcome measure was progression-free survival (PFS) determined by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST v1.1). Additional efficacy outcome measures were overall survival (OS) and overall response rate (ORR) determined by BICR using RECIST v1.1. Tumor assessments were conducted 12 weeks after randomization and continued every 8 weeks up to week 52 and then every 12 weeks.

The trial population characteristics were: median age 63 years (range: 20 to 94); 58% male; 97% White 0.7% African American, and American Indian/Alaskan Native 0.1%; Hispanic 7%; and ECOG performance score was 0 (67%) or 1 (33%). Disease characteristics were: PD-L1 expression ≥1% (41%), LAG-3 expression ≥1% (75%), AJCC Stage IV disease (92%), M1c disease (39%); M1d disease (2.4%), elevated LDH (36%), and BRAF V600 mutation-positive melanoma (39%).

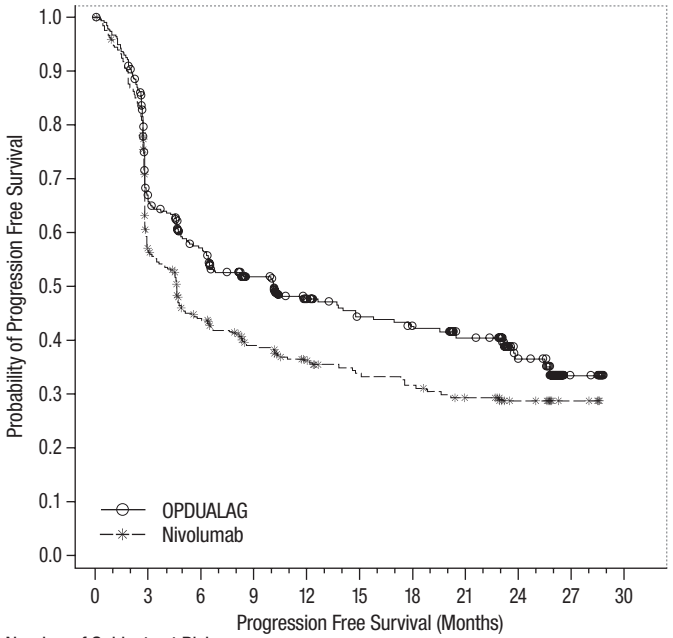
The trial demonstrated a statistically significant improvement in PFS for patients randomized to the OPDUALAG arm compared with the nivolumab arm. The final analysis of OS was not statistically significant. Efficacy results are shown in Table 5 and Figure 1.

Table 5: Efficacy Results in RELATIVITY-047

	OPDUALAG N=355	Nivolumab N=359
Progression-free Survival[a,b]		
Disease progression or death (%)	180 (51)	211 (59)
Median (months)[c] (95% CI)	10.1 (6.4, 15.7)	4.6 (3.4, 5.6)
Hazard ratio[d] (95% CI)	0.75 (0.62, 0.92)	
p-value[e]	0.0055	
Overall Survival[f]		
Deaths (%)	137 (39)	160 (45)
Median in months (95% CI)	NR (34.2, NR)	34.10 (25.2, NR)
Hazard ratio[d] (95% CI)	0.80 (0.64, 1.01)	
p-value[e]	NS[g]	
Overall Response Rate[a,f,h], n (%)	153 (43)	117 (33)
(95% CI)	(38, 48)	(28, 38)
Complete response rate (%)	58 (16)	51 (14)
Partial response rate (%)	95 (27)	66 (18)

[a] Assessed by BICR.
[b] Final PFS analysis.
[c] Kaplan-Meier estimate.
[d] Based on stratified Cox proportional hazard model.
[e] Based on stratified log-rank test.
[f] At the time of the final OS analysis, which was event-driven and occurred after the final PFS analysis.
[g] Not Significant at alpha level 0.04302.
[h] Not formally tested based on the testing hierarchy.
NR = Not reached.

Figure 1: Progression-free Survival - RELATIVITY-047



16 HOW SUPPLIED/STORAGE AND HANDLING

OPDUALAG (nivolumab and relatlimab-rmbw) injection is a sterile, preservative-free, clear to opalescent, colorless to slightly yellow solution for intravenous use supplied in a single-dose vial containing 240 mg of nivolumab and 80 mg of relatlimab per 20 mL (12 mg and 4 mg per mL) per carton (NDC 0003-7125-11).

Store OPDUALAG refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of use. Do not freeze or shake.

OPDUALAG™ (nivolumab and relatlimab-rmbw)

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Immune-Mediated Adverse Reactions (IMAR)

Inform patients of the risk of IMARs that may require corticosteroid treatment and withholding or discontinuation of OPDUALAG, including:

- Pneumonitis: Advise patients to contact their healthcare provider immediately for any new or worsening cough, chest pain, or shortness of breath *[see Warnings and Precautions (5.1)]*.
- Colitis: Advise patients to contact their healthcare provider immediately for diarrhea or severe abdominal pain *[see Warnings and Precautions (5.1)]*.
- Hepatitis: Advise patients to contact their healthcare provider immediately for jaundice, severe nausea or vomiting, pain on the right side of abdomen, lethargy, or easy bruising or bleeding *[see Warnings and Precautions (5.1)]*.
- Endocrinopathies: Advise patients to contact their healthcare provider immediately for signs or symptoms of hypophysitis, adrenal insufficiency, thyroiditis, hypothyroidism, hyperthyroidism, and diabetes mellitus *[see Warnings and Precautions (5.1)]*.
- Nephritis with Renal Dysfunction: Advise patients to contact their healthcare provider immediately for signs or symptoms of nephritis, including decreased urine output, blood in urine, swelling in ankles, loss of appetite, and any other symptoms of renal dysfunction *[see Warnings and Precautions (5.1)]*.
- Skin Adverse Reactions: Advise patients to contact their healthcare provider immediately for rash *[see Warnings and Precautions (5.1)]*.
- Myocarditis: Advise patients to contact their healthcare provider immediately for signs or symptoms of new or worsening chest pain, palpitations, shortness of breath, fatigue, or swelling in ankles *[see Warnings and Precautions (5.1)]*.

Infusion-Related Reactions

- Advise patients of the potential risk of infusion-related reactions *[see Warnings and Precautions (5.2)]*.

Complications of Allogeneic HSCT

- Advise patients of potential risk of post-transplant complications *[see Warnings and Precautions (5.3)]*.

Embryo-Fetal Toxicity

- Advise females of reproductive potential of the potential risk to a fetus and to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.4), Use in Specific Populations (8.1)]*.
- Advise females of reproductive potential to use effective contraception during treatment with OPDUALAG and for at least 5 months following the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

- Advise women not to breastfeed during treatment with OPDUALAG and for 5 months after the last dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
U.S. License No. 1713

MEDICATION GUIDE

OPDUALAG™ (op-DEW-uh-lag)
(nivolumab and relatlimab-rmbw)
injection

What is the most important information I should know about OPDUALAG?

OPDUALAG is a medicine that may treat a type of skin cancer called melanoma by working with your immune system. OPDUALAG can cause your immune system to attack normal organs and tissues in any area of your body and can affect the way they work. These problems can sometimes become severe or can lead to death. These problems may happen anytime during treatment or even after your treatment has ended. You may have more than one of these problems at the same time.

Call or see your healthcare provider right away if you develop any new or worse signs of symptoms, including:

Lung problems.

- new or worsening cough
- shortness of breath
- chest pain

Intestinal problems.

- diarrhea (loose stools) or more frequent bowel movements than usual
- stool that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdominal) pain or tenderness

Liver problems.

- yellowing of your skin or the whites of your eyes
- severe nausea or vomiting
- pain on the right side of your stomach area (abdomen)
- dark urine (tea colored)
- bleeding or bruising more easily than normal

Hormone gland problems.

- headaches that will not go away or unusual headaches
- eye sensitivity to light
- eye problems
- rapid heartbeat
- increased sweating
- extreme tiredness
- weight gain or weight loss
- feeling more hungry or thirsty than usual
- urinating more often than usual
- hair loss
- feeling cold
- constipation
- your voice gets deeper
- dizziness or fainting
- changes in mood or behavior, such as decreased sex drive, irritability, or forgetfulness

Kidney problems.

- decrease in your amount of urine
- blood in your urine
- swelling in your ankles
- loss of appetite

Skin problems.

- rash
- itching
- skin blistering or peeling
- painful sore or ulcers in mouth or nose, throat, or genital area

Heart problems.

- new or worse chest pain
- irregular heartbeat or feel like your heart is racing
- shortness of breath
- tiredness
- swelling in your ankles

Problems can also happen in other organs and tissues. These are not all of the signs and symptoms of immune system problems that can happen with OPDUALAG. Call or see your healthcare provider right away for any new or worsening sign or symptoms, which may include:

- Confusion, sleepiness, memory problems, changes in mood or behavior, stiff neck, balance problems, tingling or numbness of the arms or legs
- Double vision, blurry vision, sensitivity to light, eye pain, changes in eyesight
- Persistent or severe muscle pain or weakness, muscle cramps
- Low red blood cells, bruising

OPDUALAG™ (nivolumab and relatlimab-rmbw)

Getting medical treatment right away may keep these problems from becoming more serious.

Your healthcare provider will check you for these problems during treatment with OPDUALAG. Your healthcare provider may treat you with corticosteroid or hormone replacement medicines. Your healthcare provider may also need to delay or completely stop treatment with OPDUALAG, if you have severe side effects.

What is OPDUALAG?

OPDUALAG is a prescription medicine used to treat:

- adults and children 12 years of age or older with a type of skin cancer called melanoma that has spread or cannot be removed by surgery.

It is not known if OPDUALAG is safe and effective when used:

- in children 12 years of age or older who weigh less than 88 pounds (40 kg), or
- in children younger than 12 years of age.

Before you receive OPDUALAG, tell your healthcare provider if you:

- have immune system problems such as Crohn's disease, ulcerative colitis, or lupus
- have received an organ transplant
- have received or plan to receive a stem cell transplant that uses donor stem cells (allogeneic)
- have a condition that affects your nervous system, such as myasthenia gravis or Guillain-Barré syndrome
- are pregnant or plan to become pregnant. OPDUALAG can harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start receiving OPDUALAG.
  - You should use an effective method of birth control during and for at least 5 months after the last dose of OPDUALAG. Talk to your healthcare provider about birth control methods that you can use during this time.
  - Tell your healthcare provider right away if you become pregnant during treatment with OPDUALAG.
- are breastfeeding or plan to breastfeed. It is not known if OPDUALAG passes into your breast milk. Do not breastfeed during treatment with OPDUALAG and for 5 months after the last dose of OPDUALAG.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive OPDUALAG?

- Your healthcare provider will give you OPDUALAG into your vein through an intravenous (IV) line over 30 minutes.
- OPDUALAG is usually given every 4 weeks.
- Your healthcare provider will decide how many treatments you need.
- Your healthcare provider will do blood tests to check you for side effects.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of OPDUALAG?

OPDUALAG can cause serious side effects, including:

- **See "What is the most important information I should know about OPDUALAG?"**
- **Severe infusion reactions.** Tell your healthcare provider or nurse right away if you get these symptoms during an infusion of OPDUALAG:
  - chills or shaking
  - itching or rash
  - flushing
  - shortness of breath
  - dizziness
  - feel like passing out
  - fever
  - back or neck pain
- **Complications of stem cell transplant that uses donor stem cells (allogeneic).** These complications can be severe and can lead to death. These complications may happen if you underwent transplantation either before or after being treated with OPDUALAG. Your healthcare provider will monitor you for signs of complications if you have an allogeneic stem cell transplant.

OPDUALAG™ (nivolumab and relatlimab-rmbw)

The most common side effects of OPDUALAG include:

- muscle and bone pain
- tiredness
- decreased red blood cell and white blood cell counts
- increased liver function test results
- rash
- itching
- diarrhea
- decreased salt (sodium) in your blood

These are not all the possible side effects of OPDUALAG.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of OPDUALAG.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or healthcare provider for information about OPDUALAG that is written for health professionals.

What are the ingredients in OPDUALAG?

Active ingredients: nivolumab and relatlimab

Inactive ingredients: histidine, L-histidine hydrochloride monohydrate, pentetic acid, polysorbate 80, sucrose, and Water for Injection.

Manufactured by: Bristol-Myers Squibb Company Princeton, NJ 08543 USA U.S. License No. 1713

For more information, call 1-855-673-4861 or go to www.OPDUALAG.com.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Revised: March 2022

1425-US-2400035 03/24

Bristol Myers Squibb®