NEW DRUG APPROVAL

Brand Name	Opdualag™
Generic Name	nivolumab and relatlimab-rmbw
Drug Manufacturer	Bristol-Myers Squibb Company

New Drug Approval

FDA approval date: March 18, 2022

Review designation: N/A; Orphan

Type of review: Biologic License Application **(**BLA) 761234

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Melanoma is a malignant tumor that arises from uncontrolled proliferation of melanocytes—pigment-producing cells. While the most common form of melanoma is cutaneous, it can also arise in mucosal surfaces, the uveal tract, and leptomeninges.

Malignant melanoma is the most lethal form of skin cancer. Historically, melanoma was a rare cancer, but in the last 50 years its incidence has risen faster than almost any other cancer. The worldwide incidence of melanoma has risen rapidly over the course of the last 50 years. Its incidence is greatest among fair-skinned populations, and in regions of lower latitude. Incidence is greater among geriatric populations, but melanoma is also among the most common cancers found in adolescent and young adult populations. In fact, it is one of the leading cancers in average years of life lost per death from disease. Melanoma incidence varies by sex, which is also associated with differences in melanoma anatomic site. Similar differences by region, ethnicity, age, and sex are observed in mortality rates of melanoma.

In 2017, approximately 87,110 individuals are predicted to be diagnosed with melanoma in the United States alone. While it still represents less than 5% of all cutaneous malignancies, melanoma accounts for most skin cancer deaths. If melanoma is diagnosed in its early stages, resection of the lesion is associated with favourable survival rates. However, melanoma is an aggressive malignancy that tends to metastasize beyond its primary site. Once melanoma is advanced, surgery is no longer sufficient, and the disease becomes more difficult to treat. In the United States alone, the annual costs of melanoma treatment have risen by 288% in less than a decade. As new expensive pharmacologic treatments come to market, costs will likely rise at even greater rates. Melanoma comprises $3.3 billion of the total $8.1 billion in all direct skin cancer annual costs. Indirect costs associated with melanoma are estimated to be as high as over $3.5 billion annually. As incidence and mortality rises, costs for treatment and indirect care are projected to concurrently rise.

Efficacy

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 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%).

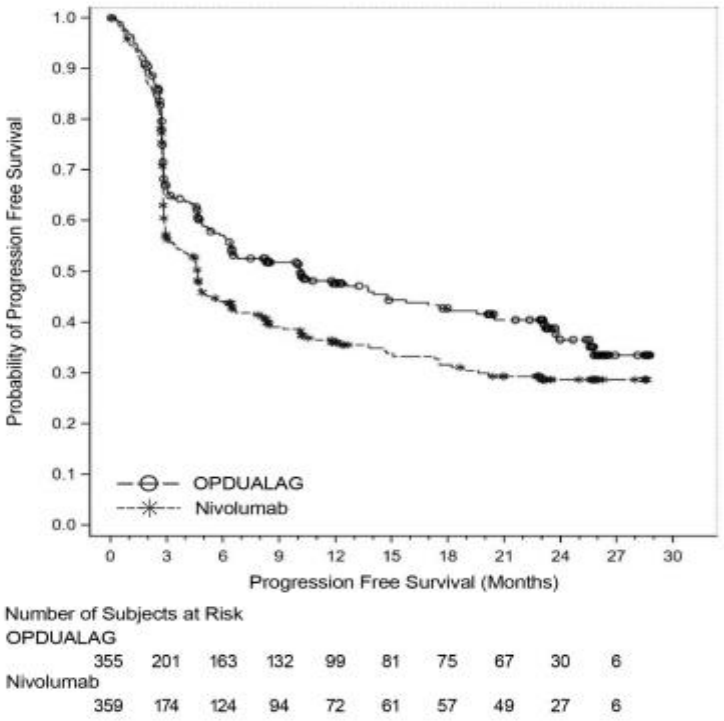
The trial demonstrated a statistically significant improvement in PFS for patients randomized to the Opdualag™ arm compared with the nivolumab arm. The final analysis of OS was not statistically significant. Efficacy results are shown below:

Table 1: 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



Safety

ADVERSE EVENTS

Serious adverse reactions occurred in 36% of patients treated with Opdualag™. The most frequent serious adverse reactions reported in ≥1% of patients 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%); 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%).

WARNINGS & PRECAUTIONS

- **Severe and Fatal Immune-Mediated Adverse Reactions**- Potentially breaks peripheral tolerance and induces 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, IMARs can also manifest after discontinuation.

- **Immune-Mediated Pneumonitis**- 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**- 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**- 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**- Can cause primary or secondary adrenal insufficiency. For Grade 2 or higher adrenal insufficiency, initiate symptomatic treatment, including hormone replacement as clinically indicated. 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 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. 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.
  - **Thyroid Disorders-** 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.
  - **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.
  - **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.

- **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.
- **Type 1 Diabetes Mellitus, which can present with Diabetic Ketoacidosis**- 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**- Can cause immune-mediated nephritis, which is defined as requiring use of steroids and no clear alternate etiology. 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.
- **Immune-Mediated Dermatologic Adverse Reactions**- 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. 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.
- **Immune-Mediated Myocarditis**- 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. 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.
- **Infusion-Related Reactions**- 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.
- **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). These complications may occur despite intervening therapy between PD-1/PD-L1 blockade and 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.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS 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 pathwaymediated 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.

Dose & Administration

ADULTS

The recommended dosage for adult patients 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.

PEDIATRICS

The recommended dosage for pediatric patients 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.

GERIATRICS

Refer to adult dosing.

RENAL IMPAIRMENT

Altered kidney function prior to treatment initiation:

- eGFR 30 to 89 mL/minute/1.73 m^2: There are no dosage adjustment.
- eGFR <30 mL/minute/1.73 m^2: There are no dosage adjustment.

Nephritis with kidney dysfunction during treatment (immune-mediated nephritis):

- If nivolumab/relatlimab treatment interruption or discontinuation is required, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone [or equivalent]) or other appropriate therapy for immune-mediated adverse reactions until improvement to ≤ grade 1, then follow with a corticosteroid taper and continue to taper over at least 1 month.
- Grade 2 or grade 3 serum creatinine elevation: Withhold nivolumab/relatlimab; resume after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue nivolumab/relatlimab if no complete or partial response within 12 weeks of last nivolumab/relatlimab dose, or if unable to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of corticosteroid initiation.
- Grade 4 serum creatinine elevation: Permanently discontinue nivolumab/relatlimab.

HEPATIC IMPAIRMENT

Hepatic impairment prior to treatment initiation:

- Mild (total bilirubin ≤ ULN and AST > ULN or total bilirubin >1 to 1.5 × ULN and any AST) or moderate (total bilirubin >1.5 to 3 × ULN and any AST) impairment: There are no dosage adjustment.
- Severe impairment (total bilirubin >3 × ULN and any AST): There are no dosage adjustment.

Hepatotoxicity during treatment (immune-mediated hepatitis):

- If nivolumab/relatlimab treatment interruption or discontinuation is required, administer systemic corticosteroids (1 to 2 mg/kg/day prednisone [or equivalent]) or other appropriate therapy for immune-mediated adverse reactions until improvement to ≤ grade 1, then follow with a corticosteroid taper and continue to taper over at least 1 month.
- AST, ALT increases to >3 to ≤8 × ULN or total bilirubin >1.5 to ≤3 × ULN: Withhold nivolumab/relatlimab; resume after complete or partial (to grade 0 or 1) resolution after corticosteroid taper. Permanently discontinue nivolumab/relatlimab if no complete or partial response within 12 weeks of last nivolumab/relatlimab dose, or if unable to reduce prednisone to ≤10 mg/day (or equivalent) within 12 weeks of corticosteroid initiation.
- AST or ALT >8 × ULN (regardless of baseline) or total bilirubin >3 × ULN: Permanently discontinue nivolumab/relatlimab.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

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.