Medical Policy

Healthcare Services Department

Policy Name	Policy Number	Scope
Nivolumab and relatlimab-rmbw (Opdualag®)	MP-RX-FP-67-23	☒ MMM MA ☒ MMM Multihealth

Service Category

☐ Anesthesia
☐ Surgery
☐ Radiology Procedures
☐ Pathology and Laboratory Procedures
☐ Medicine Services and Procedures
☐ Evaluation and Management Services
☐ DME/Prosthetics or Supplies
☒ Part B DRUG

Service Description

This document addresses the use of Opdualag®, a combination of novolumab, a programmed death receptor-1 (PD-1) blocking antibody, and relatlimab-rmbw, a lymphocyte activation gene-3 (LAG-3) blocking antibody, approved by the Food and Drug Administration (FDA) for the treatment of adult and pediatric patients 12 years of age or older with unresectable or metastatic melanoma.

Background Information

Nivolumab and relatlimab-rmbw are combined in Opdualag (Bristol-Myers Squibb Company), forming a fixed-dose blend of two IgG4 kappa monoclonal antibodies (mAbs). These include nivolumab, a programmed death receptor-1 (PD-1) blocking antibody, and relatlimab, a lymphocyte activation gene-3 (LAG-3) blocking antibody. Nivolumab functions by binding to the PD-1 receptor, disrupting its interaction with ligands like PD-L1 and PD-L2, thereby reducing PD-1 pathway-mediated immune response inhibition, including anti-tumor immune response. On the other hand, relatlimab binds to the LAG-3 receptor, hindering interactions with its ligands, including major histocompatibility Class-II (MHC II), and reducing LAG-3 pathway-mediated immune response inhibition. The synergistic effect of nivolumab (anti-PD-1) and relatlimab (anti-LAG-3) enhances T-cell activation compared to their individual actions (Bristol-Myers Squibb, 2022).

According to the prescribing information, it is important to note the following warnings and precautions associated with nivolumab and relatlimab-rmbw (Opdualag):

- Immune-Mediated Adverse Reactions: These reactions can be severe or even life-threatening and may affect various organ systems or tissues. They include immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, dermatologic adverse reactions, nephritis with renal dysfunction, and myocarditis.
- Infusion-Related Reactions: Infusion-related reactions may also be severe or life-threatening.
- Complications of Allogeneic Hematopoietic Stem Cell Transplantation (HSCT): Serious or fatal complications can occur, including 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).
- Embryo-Fetal Toxicity: This medication has the potential to cause harm to a developing fetus and should be avoided during pregnancy.

Opdualag received approval from the FDA on March 18, 2022. This fixed-dose combination is indicated for the treatment of unresectable or metastatic melanoma in patients aged 12 years and older. Opdualag earned FDA

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recognition with priority review, fast track designation, and orphan drug designation. The FDA's decision to approve Opdualag was informed by compelling data derived from the RELATIVITY-047 study (FDA, 2022).

In the RELATIVITY-047 study, researchers assessed the safety and effectiveness of the fixed-dose combination of nivolumab and relatlimab in comparison to nivolumab alone. The trial involved 714 patients with previously untreated metastatic or unresectable melanoma, randomly assigned to receive either nivolumab 480 mg and relatlimab 160 mg or nivolumab 480 mg alone via intravenous infusion every 4 weeks until disease progression or unacceptable side effects.

The primary measure of effectiveness was progression-free survival (PFS), with secondary endpoints including overall survival (OS) and overall response rate (ORR). The results showed that nivolumab and relatlimab combination therapy significantly extended median PFS to 10.1 months, compared to 4.6 months with nivolumab alone (HR for progression or death, 0.75 [95% CI, 0.62 to 0.92]; p=0.006). The 12-month PFS rate was also higher in the combination group (47.7% vs. 36.0%).

Nivolumab and relatlimab demonstrated consistent benefits across various patient subgroups. Grade 3 or 4 treatment-related adverse events were observed in 18.9% of the combination therapy group and 9.7% of the nivolumab-only group. Additionally, treatment-related adverse events leading to discontinuation were more frequent in the combination arm (14.6% vs. 6.7% in the nivolumab group).

In conclusion, the combination of nivolumab and relatlimab, targeting both LAG-3 and PD-1 checkpoints, offered superior progression-free survival benefits compared to PD-1 inhibition alone in previously untreated metastatic or unresectable melanoma patients. Importantly, no new safety concerns were identified with the combination therapy.

Definitions and Measures

- Adjuvant therapy: Treatment given after the primary treatment to increase the chances of a cure; may include chemotherapy, radiation, hormone or biological therapy.
- BRAF: The oncogene which directions production of a protein in the regulating MAP kinase/ERKs signaling pathway, which affects cell division, differentiation, and secretion.
- Disease Progression: Cancer that continues to grow or spread.
- ECOG or Eastern Cooperative Oncology Group Performance Status: A scale and criteria used by doctors and researchers to assess how an individual's disease is progressing, assess how the disease affects the daily living abilities of the individual, and determine appropriate treatment and prognosis. This scale may also be referred to as the WHO (World Health Organization) or Zubrod score which is based on the following scale:
    - 0 = Fully active, able to carry on all pre-disease performance without restriction
    - 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work

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  - 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
  - 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
  - 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
  - 5 = Dead
- Immune checkpoint inhibitor: A type of drug that blocks certain proteins made by some types of immune system cells, such as T cells, and some cancer cells. When these proteins are blocked, the "brakes" on the immune system are released and T cells are able to kill cancer cells better. Examples of checkpoint proteins found on T cells or cancer cells include programmed death (PD)-1, PD-ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen (CTLA)-4/B7-1/B7-2 (NCI, 2018).
- Kinase inhibitor: Type of drug which works by blocking several enzymes that promote cell growth, which has been found to be an effective approach to treat a variety of cancers.
- Melanoma: A type of cancer that begins in the melanocytes. Melanoma is also referred to as malignant melanoma and cutaneous melanoma.
- Metastasis: The spread of cancer from one part of the body to another; a metastatic tumor contains cells that are like those in the original (primary) tumor and have spread.
- Neoadjuvant therapy: Treatment given as a first step to shrink a tumor before the main treatment, which is usually surgery, is given. Examples of neoadjuvant therapy include chemotherapy, radiation therapy, and hormone therapy. It is a type of induction therapy.
- Primary refractory disease: Cancer that does not respond at the beginning of treatment; may also be called resistant disease.
- Progressive Disease (PD): Cancer that is growing, spreading, or getting worse. Refractory Disease: Illness or disease that does not respond to treatment.
- Stable disease: Cancer that is not decreasing or increasing in extent or severity.

Approved Indications

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

Other Uses

None

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Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

HCPCS	Description
J9298	Injection, nivolumab and relatlimab-rmbw, 3 mg/1 mg [Opdualag]

ICD-10	Description
C43.0	Malignant melanoma of lip
C43.10-C43.12	Malignant melanoma of eyelid, including canthus
C43.111	Malignant melanoma of right upper eyelid, including canthus
C43.112	Malignant melanoma of right lower eyelid, including canthus
C43.121	Malignant melanoma of left upper eyelid, including canthus
C43.122	Malignant melanoma of left lower eyelid, including canthus
C43.20-C43.22	Malignant melanoma of ear and external auricular canal
C43.30	Malignant melanoma of unspecified part of face
C43.31	Malignant melanoma of nose
C43.39	Malignant melanoma of other parts of face
C43.4	Malignant melanoma of scalp and neck
C43.51	Malignant melanoma of anal skin
C43.52	Malignant melanoma of skin of breast
C43.59	Malignant melanoma of other part of trunk
C43.60-C43.62	Malignant melanoma of unspecified upper limb, including shoulder
C43.70-C43.72	Malignant melanoma of lower limb, including hip
C43.8	Malignant melanoma of overlapping sites of skin
C43.9	Malignant melanoma of skin, unspecified

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Medical Necessity Guidelines

When a drug is being reviewed for coverage under a member's medical benefit plan or is otherwise subject to clinical review (including prior authorization), the following criteria will be used to determine whether the drug meets any applicable medical necessity requirements for the intended/prescribed purpose.

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

Nivolumab and relatlimab-rmbw (Opdualag®)

A. Criteria For Initial Approval

i. Individual is 12 years of age or older and weighing at least 40 kg (Label; Tawbi HA et.al. 2022, NCCN 1); **AND**
ii. Individual has a diagnosis of unresectable or metastatic (Stage III or IV) melanoma; **AND**
iii. Individual has an Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 or a Lansky performance score ≥ 80% for minors (12 to 17 years of age).

B. Criteria For Continuation of Therapy

i. MMM considers continuation of Nivolumab and relatlimab-rmbw (Opdualag®) therapy medically necessary in members requesting reauthorization for an indication listed in Section A above (Criteria for Initial Approval) when there is no evidence of an unacceptable toxicity or disease progression while on the current regimen. The following information should be submitted for reauthorization:
    A. A current oncology note documenting the patient's response to treatment showing no progression of disease
    B. Current imaging studies and other objective measures, as appropriate, showing no progression of disease when compared with previous results

C. Authorization Duration

i. Initial Approval Duration: Up to 6 months
ii. Reauthorization Approval Duration: Up to 6 months

D. **Conditions Not Covered**

Any other use is considered experimental, investigational, or unproven, including the following (this list may not be all inclusive):

i. Uveal melanoma;
ii. Active brain metastases or leptomeningeal metastases;

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iii. When the above criteria (Section A: Criteria for Initial Approval) are not met, and for all other indications.

Limits or Restrictions

A. Quantity Limitations

Approvals may be subject to dosing limits in accordance with FDA-approved labeling, accepted compendia, and/or evidence-based practice guidelines. The chart below includes dosing recommendations as per the FDA-approved prescribing information.

Drug	Recommended Dosing Schedule	Treatment Duration
Nivolumab and relatlimab-rmbw (Opdualag®)	Adult patients and pediatric patients ≥ 12 years who weigh at least 40 kg: 480 mg nivolumab and 160 mg relatlimab i.v. every 4 weeks. [a]	Until disease progression or unacceptable toxicity.
Exceptions		
• The recommended dosage for pediatric patients 12 years of age or older who weigh less than 40 kg has not been established.		

[a] Product is available as a single dose vial consisting of 240 mg nivolumab and 80 mg relatlimab per 20 mL (12 mg and 4 mg per mL). Two single dose vials (40 mL) are needed to complete the recommended dose of 480 mg nivolumab and 160 mg relatlimab.

Reference Information

1. Bristol-Myers Squibb Company, Opdualag (nivolumab and relatlimab-rmbw) injection, for intravenous use. Prescribing Information. Princeton, NJ: Bristol-Myers Squibb: March 2022.
2. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med. 2022;386(1):24-34.
3. U.S. Food and Drug Administration (FDA). FDA approves Opdualag for unresectable or metastatic melanoma. Drugs. Silver Spring, MD: FDA; March 21, 2022.
4. Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.: 2023. URL: http://www.clinicalpharmacology.com. Updated periodically.
5. DailyMed. Package inserts. U.S. National Library of Medicine, National Institutes of Health website. http://dailymed.nlm.nih.gov/dailymed/about.cfm. Accessed: July 8, 2023
6. DrugPoints® System [electronic version]. Truven Health Analytics, Greenwood Village, CO. Updated periodically.
7. Lexi-Comp ONLINE™ with AHFS™, Hudson, Ohio: Lexi-Comp, Inc.; 2023; Updated periodically.

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8. NCCN Clinical Practice Guidelines in Oncology™. © 2023 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: http://www.nccn.org/index.asp. Accessed on July 8, 2023.
    a. Melanoma: Cutaneious V2.2023. Revised March 10, 2023.
9. Tawbi HA, Schadendorf D, Lipson EJ, et al. Relatlimab and Nivolumab versus Nivolumab in Untreated Advanced Melanoma. N. Engl J Med.2022;386(1):24-34. Accessed July 8, 2023

Federal and state laws or requirements, contract language, and Plan utilization management programs or polices may take precedence over the application of this clinical criteria.

Policy History

Revision Type	Summary of Changes	P&T Approval Date	MPCC Approval Date
Policy Inception	Elevance Health's Medical Policy adoption.	N/A	11/30/2023

Revised: 11/11/2023