**CLINICAL GUIDELINES FOR MEDICAL NECESSITY**

**MEDICAL POLICY**

# Cemiplimab-rwlc (Libtayo®)

Version: 1.0

**EFFECTIVE DATE: 1/1/2024**

NantHealth® | Eviti®

## Please note the following:

## Cemiplimab-rwlc (Libtayo®)

**Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Please refer to the CMS website at http://www.cms.gov for additional information.**

**Note: For Medicaid members/enrollees, circumstances when state Medicaid coverage provisions conflict with the coverage provisions within this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.**

## Cemiplimab-rwlc (Libtayo): Discussion

Cemiplimab-rwlc is a recombinant human immunoglobulin G4 (IgG4) monoclonal antibody that binds to PD-1 and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. [1]

The binding of the PD-1 ligands PD-L1 and PD-L2 to the PD-1 receptor found on T-cells inhibits T-cell growth and cytokine production. Upregulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to the inhibition of active T-cell immune surveillance of tumors. [1]

Cemiplimab-rwlc can cause immune-mediated adverse reactions, which may be severe or fatal and can occur in any organ system or tissue. Immune-mediated adverse reactions can occur at any time after starting PD-1/PD-L1 blocking antibody. While immune-mediated adverse reactions usually manifest during treatment with PD-1/PD-L1 blocking antibodies, immune-mediated adverse reactions can also manifest after discontinuation of PD-1/PD-L1 blocking antibodies. Immune-mediated adverse reactions affecting more than one body system can occur simultaneously. [1]

Cemiplimab-rwlc is approved by the Food and Drug Administration (FDA) for the treatment of:

1. Cutaneous squamous cell carcinoma (CSCC) - For the treatment of patients with metastatic cutaneous squamous cell carcinoma (mCSCC) or locally advanced CSCC (laCSCC) who are not candidates for curative surgery or curative radiation.
2. Basal cell carcinoma (BCC) - For the treatment of patients with locally advanced or metastatic BCC (laBCC or mBCC) who have been previously treated with a hedgehog pathway inhibitor or for whom a hedgehog pathway inhibitor is not appropriate.
3. Non-small cell lung cancer (NSCLC)
    a) In combination with platinum-based chemotherapy for the first-line treatment of adult patients with non-small cell lung cancer (NSCLC) with no EGFR, ALK or ROS1 aberrations and is:
        i. Locally advanced where patients are not candidates for surgical resection or definitive chemoradiation; or metastatic disease.

b) As a single agent for the first-line treatment of adult patients with NSCLC whose tumors have high PD-L1 expression [Tumor Proportion Score (TPS) ≥50%], with no EGFR, ALK or ROS1 aberrations, and is:
   i. Locally advanced where patients are not candidates for surgical resection or definitive chemoradiation, or metastatic disease. [1]

The National Comprehensive Cancer Network (NCCN) endorses cemiplimab-rwlc for the following cancer types: basal cell skin cancer, non-small cell lung cancer, and squamous cell skin cancer. [2,3,4]

## Cemiplimab-rwlc: Definitions

- **Food and Drug Administration (FDA)** – The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.
- **Hedgehog pathway inhibitor –** A relatively new class of drugs that act by targeting the proteins involved in the regulation of the Hedgehog (Hh) pathway. The Hh proteins comprise a group of secreted proteins that regulate cell growth, differentiation, and survival. [5]
- **Immune checkpoint inhibitors (ICIs) -** Immunotherapy drugs called immune checkpoint inhibitors work by blocking checkpoint proteins from binding with their partner proteins. This prevents the "off" signal from being sent, allowing the T cells to kill cancer cells. One such drug acts against a checkpoint protein called CTLA-4. Other immune checkpoint inhibitors act against a checkpoint protein called PD-1 or its partner protein PD-L1. [6]
- **Immune-mediated adverse reactions (IMARs) -** Immune checkpoint proteins, such as cytotoxic T-lymphocyte antigen-4 and programmed death-1, are part of the normal immune system and regulate immune activation. Treatment with inhibitors for these checkpoint proteins can result in adverse reactions that present similarly to other conditions. These immune-mediated adverse reactions (IMARs) are most commonly gastrointestinal, respiratory, endocrine, or dermatologic. More rarely, neurologic, ocular, cardiovascular, hematologic, and renal IMARs can occur. The median time to onset of IMARs with anti-PD-1/PD-L1 antibodies is typically between 1 and 6 months; however, IMARs again may present as late as 41 months after treatment initiation. For ipilimumab (anti-CTLA-4), dermatologic IMARs typically present after 2–3 weeks of treatment, while GI and hepatic IMARs appear after 6–7 weeks and some endocrinopathies can appear 9 weeks or later after immunotherapy.[7]
- **National Comprehensive Cancer Network (NCCN) -** An alliance of 32 leading cancer centers devoted to patient care, research, and education. The NCCN guidelines are utilized for Radiation Therapy and Medical Oncology standards. NCCN consensus clinical standards are periodically updated and NantHealth, Inc. reviews these and updates its policies within a timely manner.

- **Oncogenic drivers –** Genes whose mutation facilitates tumor growth are called driver genes. Cancer develops because of the accumulation of a somatic (after conception) mutation and other genetic alterations that impair cell division, checkpoints, etc., which result in abnormal cell proliferation and eventually cancer. Such mutations are called "driver mutations".[8] The discovery of oncogenic drivers led to the design of therapies targeting tumors harboring specific gene alterations that cause aberrant signaling and growth. [9]
- **Programmed cell death protein 1 (PD-1)/Programmed cell death-ligand 1 (PD-L1) –** Checkpoint proteins, such as PD-L1 on tumor cells and PD-1 on T cells, help keep immune responses in check. The binding of PD-L1 to PD-1 keeps T cells from killing tumor cells in the body. Blocking the binding of PD-L1 to PD-1 with an immune checkpoint inhibitor (anti-PD-L1 or anti-PD-1) allows the T cells to kill tumor cells. [6]

## Cemiplimab-rwlc: Policy

Cemiplimab-rwlc will be considered for coverage when the following criteria are met:

**Note:** Individuals receiving PD-1 or PD-L1 therapy should NOT be receiving therapy for an autoimmune disease or chronic condition with a systemic immunosuppressant.

### Basal Cell Skin Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. As a single agent for one of the following:
    a) Locally advanced (extensive) disease where surgery and/or radiation therapy (RT) are unlikely to result in a cure or are not feasible
    b) Nodal or regional disease, especially if surgery and RT are not feasible
    c) Distant metastatic disease, especially if surgery and RT are not feasible.

**Note:** Recommended if previously treated with a hedgehog pathway inhibitor (HHI) or for patients where an HHI is not appropriate. [2]

### Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. No progression on prior therapy with a PD-1 or PD-L1 inhibitor; AND
4. Treatment as a single agent for recurrent, advanced, or metastatic disease for PD-L1 expression positive (≥50%) tumors and negative for actionable molecular biomarkers and no contraindications to PD-1 or PD-L1 inhibitors, and a performance status of 0-2; OR
5. Treatment for recurrent, advanced, or metastatic disease as first-line therapy for PD-L1 expression-positive (≥1%) tumors that are negative for actionable molecular biomarkers and no contraindications to PD-1 or PD-L1 inhibitors, and a performance status of 0-2 for one of the following:

a) In combination with paclitaxel and either carboplatin or cisplatin
b) In combination with pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology; OR

6. Treatment for recurrent, advanced, or metastatic disease for those with a performance status of 0-1 and no contraindications to PD-1 or PD-L1 inhibitors in combination with one of the following:
    a) Paclitaxel and either carboplatin or cisplatin
    b) Pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology; AND
7. The above regimens are used in any one of the following:
    a) Initial systemic therapy for PD-L1 <1% and negative for actionable molecular biomarkers
    b) First-line therapy for EGFR exon 20 mutation-positive tumors
    c) First-line therapy for KRAS G12C mutation-positive tumors
    d) First-line or subsequent therapy for BRAF V600E mutation-positive tumors
    e) First-line or subsequent therapy for NTRK1/2/3 gene fusion-positive tumors
    f) First-line or subsequent therapy for MET exon 14 skipping mutation-positive tumors
    g) First-line or subsequent therapy for RET rearrangement-positive tumors
    h) First-line therapy for ERBB2 (HER2) mutation positive tumors
    i) Subsequent therapy for EGFR exon 19 deletion or exon 21 L858R tumors and prior erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, or dacomitinib therapy
    j) Subsequent therapy for EGFR S768I, L861Q, and/or G719X mutation-positive tumors and prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib therapy
    k) Subsequent therapy for ALK rearrangement-positive tumors and prior crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib therapy
    l) Subsequent therapy for ROS1 rearrangement-positive tumors and prior crizotinib, entrectinib, or ceritinib therapy

**Note:**

1. If there is insufficient tissue to allow testing for all EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2), repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
2. Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, and some oncogenic drivers (E.g., EGFR exon 19 deletion or exon 21 L858R, ALK rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.

8. Continuation maintenance therapy as a single agent for recurrent, advanced, or metastatic disease for PD-L1 expression positive (≥50%) tumors that are negative for actionable molecular biomarkers and no contraindications to PD-1 or PD-L1 inhibitors in those with a performance status of 0-2 who achieve a response or stable disease following first-line therapy with cemiplimab-rwlc as monotherapy, or as part of combination therapy; OR

9. Continuation maintenance therapy in combination with pemetrexed for recurrent, advanced, or metastatic disease for PD-L1 expression positive (≥1%) tumors that are negative for actionable molecular biomarkers and no contraindications to PD-1 or PD-L1 inhibitors in those with a performance status of 0-2 who achieve a response or stable disease following first-line therapy with cemiplimab-rwlc, pemetrexed, carboplatin or cisplatin for non-squamous cell histology; OR
10. Continuation maintenance therapy as a single agent for recurrent, advanced, or metastatic disease for PD-L1 expression positive (≥1-49%) tumors that are negative for actionable molecular biomarkers and no contraindications to PD-1 or PD-L1 inhibitors in those with a performance status of 0-2 who achieve a response or stable disease following first-line therapy with cemiplimab-rwlc combination therapy; OR
11. Continuation maintenance therapy as a single agent (if previously received first-line cemiplimab-rwlc combination therapy) for recurrent, advanced, or metastatic disease with PD-L1 expression <1% tumors that are negative for actionable molecular biomarkers and no contraindications to PD-1 or PD-L1 inhibitors, and a performance status of 0-2 in those who achieve tumor response or stable disease following initial systemic therapy; OR
12. Continuation maintenance therapy in combination with pemetrexed (if previously received first-line cemiplimab-rwlc, pemetrexed, carboplatin or cisplatin) for recurrent, advanced, or metastatic disease with PD-L1 expression <1% tumors of non-squamous cell histology that are negative for actionable molecular biomarkers and no contraindications to PD-1 or PD-L1 inhibitors, and a performance status of 0-2 in those who achieve tumor response or stable disease following initial systemic therapy.

**Note:**

1. If there is insufficient tissue to allow testing for all EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2), repeat biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.
2. Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or current use of immunosuppressive agents, and some oncogenic drivers (E.g., EGFR exon 19 deletion or exon 21 L858R, ALK rearrangements) have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors. [3]

**Squamous Cell Skin Cancer**

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. Single-agent neoadjuvant treatment for the disease that is borderline resectable, unresectable, or if surgery may carry high morbidity; OR
4. Single-agent treatment if curative radiation therapy or surgery is not feasible for the disease that is one of the following:
    a) Locally advanced
    b) Recurrent
    c) Metastatic [4]

**Note:** Coverage of cemiplimab-rwlc will be provided for an FDA-approved indication or National Comprehensive Cancer Network (NCCN) guidelines when it is a Category 1, 2A, or 2B recommendation OR when all criteria are met.

## Authorization Period and Renewal Criteria

1. Initial Authorization Period: 12 months
2. Renewal Criteria: No evidence of disease progression or unacceptable toxicity
3. Renewal Authorization Period: 12 months

## Cemiplimab-rwlc: References


1. Libtayo® (Cemiplimab-rwlc) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761097s016lbl.pdf. Accessed June 2, 2023.
2. National Comprehensive Cancer Network Guidelines. Basal Cell Skin Cancer (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf. Accessed June 2, 2023.
3. National Comprehensive Cancer Network Guidelines. Non-Small Cell Lung Cancer (Version 3.2023). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed June 12, 2023.
4. National Comprehensive Cancer Network Guidelines. Squamous Cell Skin Cancer (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf. Accessed on June 12, 2023.
5. Infectious Agents and Cancer 2012: Hedgehog Pathway Inhibitors – Current Status and Future Prospects;7:29. https://infectagentscancer.biomedcentral.com/articles/10.1186/1750-9378-7-29. Accessed June 12, 2023.
6. National Cancer Institute. Immune Checkpoint Inhibitors; April 7, 2022. https://www.cancer.gov/about-cancer/treatment/types/immunotherapy/checkpoint-inhibitors. Accessed May 24, 2023.
7. Emerg Med J 2019: Challenge of Immune-Mediated Adverse Reactions in the Emergency Department;36:369-77. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6582806/pdf/emermed-2018-208206.pdf. Accessed May 31, 2023.
8. International Journal of Molecular and Immuno Oncology. Driver mutations in oncogenesis; May 29, 2021. https://ijmio.com/driver-mutations-in-oncogenesis. Accessed June 2, 2023.
9. National Library of Medicine. Oncogenic drivers, targeted therapies, and acquired resistance in non-small-cell lung cancer. May 23, 2014. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5696571. Accessed June 2, 2023.

## Cemiplimab-rwlc: Coding (CPT®, ICD 10 and HCPCS*)

*Procedure codes appearing in medical policy documents are only included as a general reference. This list may not be all-inclusive and is subject to updates. In addition, the codes listed are not a guarantee of payment.

| CODE | DESCRIPTION |
|---|---|
| C34.90 | Malignant neoplasm of unspecified part of unspecified lung |
| C44.319 | Basal cell carcinoma of the skin and other parts of the face |
| C44.92 | Squamous cell carcinoma of the skin |
| J9119 | Cemplimab-rwlc (Libtayo) |

## Cemiplimab-rwlc: Revision and Review History

| No. | Description | Date(s) |
|---|---|---|
| 1 | Original Effective Date: | 1/1/2024 |
| 2 | Policy Review Dates: | 6/21/2023 |
| 3 | Policy Revision Dates: | |
| 4 | Department Owner: | Medical Affairs |
| 5 | NH Advisory Committee Approval Dates: | 8/30/2023 |
| 6 | Revision Changes: | |