CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Tremelimumab-actl (Imjudo®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Tremelimumab-actl (Imjudo®)

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.

Tremelimumab-actl (Imjudo): Discussion

Tremelimumab-actl is a monoclonal antibody that attaches to a molecule called CTLA-4, which is present on the surface of T-cells (the primary immune cells involved in the killing of cancer cells). Tremelimumab-actl blocks the activity of CTLA-4, contributing to T-cell activation, priming the immune response to cancer, and fostering cancer cell death. [1, 2]

Tremelimumab-actl is a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocking antibody, indicated for:

1. In combination with durvalumab, for the treatment of adult patients with unresectable hepatocellular carcinoma (uHCC); OR
2. In combination with durvalumab and platinum-based chemotherapy for the treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) genomic tumor aberrations. [3]

The National Comprehensive Cancer Network (NCCN) endorses tremelimumab-actl in the following cancer types: hepatocellular carcinoma and non-small cell lung cancer. [4, 5]

Tremelimumab-actl: Definitions

- **Anaplastic lymphoma kinase (ALK) -** Approximately 5% of patients with NSCLC have ALK gene rearrangements and are associated with adenocarcinoma histology with no smoking history or a light smoking history. [5] ALK is a tyrosine kinase that can be aberrantly expressed in several tumor types. ALK-positive tumors (tumors harboring a rearranged ALK gene/fusion protein) are highly sensitive to therapy with ALK-targeted inhibitors.
- **BRAF V600E mutation -** BRAF is a serine/threonine kinase that is part of the MAP/ERK signaling pathway. [5] Mutations in the gene lead to unrestrained cell growth and proliferation. BRAF mutations are commonly found in the 600th codon (V600), most frequently V600E (80%) but also including V600K (15%) and a few others. BRAF V600

mutations are associated with sensitivity to BRAF inhibitors and MEK inhibitors in melanoma. [3] BRAF mutations are commonly associated with melanoma and NSCLC. The BRAF V600E mutation occurs in 1-2% of patients with lung adenocarcinoma; it is the most common of the BRAF point mutations when considered against all tumor types. Mutations in BRAF typically do not overlap with EGFR and MET exon 14 skipping mutations, RET rearrangements, ALK rearrangements, and ROS1 rearrangements. [5]

- **CTLA-4 -** A protein found on T cells (a type of immune cell) that helps keep the body's immune responses in check. [6]
- **Epidermal growth factor receptor (EGFR) -** The two most found EGFR gene mutations are deletions in exon 19 in 45% of patients and a point mutation in exon 21 (L858R in 40%). These mutations are predictive of treatment benefits from EGFR tyrosine kinase inhibitor (EGFR TKI) therapy. Most patients harboring them have adenocarcinoma histology and have either never smoked or had a light smoking history. [5]
- **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.
- **MAPK/ERK Signaling Pathway -** The extracellular-signal-regulated kinase (ERK) mitogen-activated protein kinase (MAPK) signaling pathway plays an important role in various cellular responses, including cell proliferation, cell differentiation, and cell survival. [7]
- **National Comprehensive Cancer Network (NCCN) -** An alliance of thirty-two 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.
- **ROS1 rearrangement -** A distinct receptor tyrosine kinase that is very similar to ALK and members of the insulin receptor family. It is estimated that ROS1 gene rearrangements occur in about 1-2% of patients with NSCLC. These mutations most frequently occur in nonsquamous histology but can also occur in squamous cell histology, although at a lower rate. [5]

Tremelimumab-actl: Policy

Tremelimumab-actl will be considered for coverage when the following criteria are met:

Hepatocellular Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. First-line treatment in combination with durvalumab for patients with one of the following indications:
    a) Unresectable disease and are not a transplant candidate
    b) Liver confined disease, inoperable by performance status, comorbidity, minimal, or uncertain extrahepatic disease
    c) Metastatic disease or extensive liver tumor burden [4]

Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. 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, have no contraindications to PD-1 or PD-L1 inhibitors, and have a performance status of 0-2 in combination with one of the following:
    a) Durvalumab, albumin-bound paclitaxel, and carboplatin
    b) Durvalumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology
    c) Durvalumab, gemcitabine, and either carboplatin or cisplatin for squamous cell histology; OR
4. Treatment for recurrent, advanced, or metastatic disease for patients 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) Durvalumab, albumin-bound paclitaxel, and carboplatin
    b) Durvalumab, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology
    c) Durvalumab, gemcitabine, and either carboplatin or cisplatin for squamous cell histology; AND

    The above regimens are used for one of the following:

    i. Initial systemic therapy for PD-L1 <1% and negative for actionable molecular biomarkers
    ii. First-line therapy for EGFR exon 20 mutation positive tumors
    iii. First-line therapy for KRAS G12C mutation positive tumors
    iv. First-line therapy for ERBB2 (HER2) mutation positive tumors

v. First-line or subsequent therapy for BRAF V600E mutation positive tumors
vi. First-line or subsequent therapy for NTRK1/2/3 gene fusion positive tumors
vii. First-line or subsequent therapy for MET exon 14 skipping mutation positive tumors
viii. First-line or subsequent therapy for RET rearrangement positive tumors
ix. Subsequent therapy for EGFR exon 19 deletion or exon 21 L858R tumors and prior erlotinib +/- (ramucirumab or bevacizumab), afatinib, gefitinib, osimertinib, or dacomitinib therapy
x. Subsequent therapy EGFR S768I, L861Q, and/or G719X mutation positive tumors and prior afatinib, osimertinib, erlotinib, gefitinib, or dacomitinib therapy
xi. Subsequent therapy for ALK rearrangement positive tumors and prior crizotinib, ceritinib, alectinib, brigatinib, or lorlatinib therapy
xii. 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 EGFR, KRAS, ALK, ROS1, BRAF, NTRK1/2/3, MET, RET, and ERBB2 (HER2), then repeat the biopsy and/or plasma testing should be done. If these are not feasible, treatment is guided by available results and, if unknown, the patient is to be treated as though they do not have the 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 (i.e., EGFR exon 19 deletion or exon 21 L858R, ALK rearrangements). These have been shown to be associated with less benefit from PD-1/PD-L1 inhibitors.
3. Coverage of tremelimumab-actl 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

Tremelimumab-actl: References

1. UCIR Tremelimumab-actl (Imjudo). https://www.ucir.org/immunotherapy-drugs/tremelimumab-actl. Accessed June 21, 2023.
2. Imjudo (tremelimumab) in combination with Imfinzi approved in the US for patients with unresectable liver cancer. https://www.astrazeneca.com/media-centre/press-releases/2022/imfinzi-and-imjudo-approved-in-advanced-liver-cancer.html. Accessed on June 28, 2023.
3. Tremelimumab-actl (Imjudo) Package Insert. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761270s000lbl.pdf. Accessed June 15, 2023.
4. National Comprehensive Cancer Network Guidelines. Hepatocellular Carcinoma (Version 1.2023). https://www.nccn.org/professionals/physician_gls/pdf/hcc.pdf. Accessed June 21, 2023.
5. 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 21, 2023.
6. CTLA-4. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/ctla-4. Accessed on June 26, 2023.
7. Wiley Online Library. ERK MAP kinase in G_1 cell cycle progression and cancer. https://onlinelibrary.wiley.com/doi/full/10.1111/j.1349-7006.2006.00244.x. Accessed July 12, 2023.
8. Imjudo (tremelimumab) in combination with Imfinzi approved in the US for patients with unresectable liver cancer. https://www.astrazeneca.com/media-centre/press-releases/2022/imfinzi-and-imjudo-approved-in-advanced-liver-cancer.html. Accessed on June 28, 2023.

Tremelimumab-actl: 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. CPT codes are available through the AMA.

CODE	DESCRIPTION
C22.0	Liver cell carcinoma
C34.90 – C34.92	Malignant neoplasm of unspecified part of unspecified bronchus or lung

C917, J9999	Tremelimumab-actl (Imjudo®)

Tremelimumab-actl: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	7/14/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	10/23/2023
6	Revision Changes:	