CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL ONCOLOGY

Durvalumab (Imfinzi®)

Version: 1.0

EFFECTIVE DATE: 1/1/2024

NantHealth® | Eviti®

Please note the following:

Durvalumab (Imfinzi®)

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.

Durvalumab (Imfinzi): Discussion

Durvalumab is a fully human monoclonal antibody that blocks programmed cell death ligand-1 binding to its receptors (PD-1 and CD80), resulting in enhanced recognition, and the killing of tumor cells by T- cells. [1]

A broad range of human tumors overexpress PD-L1, evading immune surveillance and antitumor T-cell responses. Thus, overexpression of PD-L1 is associated with poor prognosis. [1] PD-L1 blocks T-cell function and activation through interaction with PD-1 and CD80. By binding to its receptors, PD-L1 reduces cytotoxic T-cell activity, growth, and small protein production important in cell signaling. Durvalumab blocks or reverses PD-L1 overexpression. [2]

Durvalumab 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 (IMARs) can occur at any time after starting treatment with a 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. 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.[3]

Durvalumab is a programmed death-ligand 1 (PD-L1) blocking antibody approved by the Food and Drug Administration (FDA) for the treatment of adult patients as indicated:

1. Unresectable, stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy.
2. In combination with tremelimumab-actl and platinum-based chemotherapy, for metastatic
   non-small cell lung cancer (NSCLC) with no sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) genomic tumor aberrations.
3. In combination with etoposide and either carboplatin or cisplatin, as first-line treatment for

extensive-stage small cell lung cancer (ES-SCLC).
4. In combination with gemcitabine and cisplatin, for locally advanced or metastatic biliary tract cancer (BTC).
5. In combination with tremelimumab-actl, for unresectable hepatocellular carcinoma (uHCC). [5]

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

The National Comprehensive Cancer Network (NCCN) endorses durvalumab for the following cancer types: ampullary adenocarcinoma, biliary tract cancer, cervical cancer, hepatocellular carcinoma, non-small cell lung cancer, and small cell lung cancer. [4,5,6,7,8,9]

Durvalumab: Definitions

- **Anaplastic lymphoma kinase (ALK) rearrangement -** About 5% of patients with NSCLC have ALK gene rearrangements and are associated with adenocarcinoma histology and either a never smoking or light smoking history.[8] 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.
- **Epidermal growth factor receptor (EGFR) exon 19 deletion and epidermal growth factor receptor 21 L858R mutations -** 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. [8]
- **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.
- **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. [10]
- **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.

- **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".[12] The discovery of oncogenic drivers led to the design of therapies targeting tumors harboring specific gene alterations that cause aberrant signaling and growth. [13]
- **Programmed cell death protein 1 (PD-1)/Programmed cell death-ligand 1 (PD-LA) -** 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. [10]
- **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. [8]

Durvalumab: Policy

Durvalumab will be considered for coverage when the following criteria are met:

Ampullary Adenocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. No disease progression on prior therapy with a PD-1 or PD-L1; AND
4. First-line therapy for pancreatobiliary and mixed-type disease in patients with good performance status (ECOG 0-1, good biliary drainage, and adequate nutritional intake) in combination with gemcitabine and cisplatin for one of the following:
   a) Unresectable localized disease
   b) Stage IV resected cancer
   c) Metastatic disease at initial presentation [4]

Biliary Tract Cancers (extrahepatic cholangiocarcinoma, gallbladder cancer, and intrahepatic cholangiocarcinoma)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. No disease progression on prior therapy with a PD-1 or PD-L1; AND

4. Therapy in combination with cisplatin and gemcitabine for one of the following:
   a) Primary treatment for unresectable or resected gross residual (R2) disease, or metastatic disease
   b) Recurrent disease >6 months after surgery with curative intent and >6 months after completion of adjuvant therapy; OR
5. Subsequent treatment in combination with cisplatin and gemcitabine for progression on or after systemic treatment for unresectable or resected gross residual (R2) disease, or metastatic disease and have not received prior treatment with a checkpoint inhibitor; OR
6. Neoadjuvant chemotherapy for gallbladder cancer only in combination with cisplatin and gemcitabine for resectable locally advanced disease that presents as one of the following:
   a) Incidental finding of suspicious mass during surgery and hepatobiliary surgery expertise is unavailable
   b) Incidental finding on pathologic review
   c) Mass on imaging
   d) Jaundice [5]

Cervical Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. No disease progression on prior therapy with a PD-1 or PD-L1; AND
4. First-line or subsequent therapy (if not used previously as first-line) for persistent, recurrent, or metastatic small cell neuroendocrine carcinoma of the cervix (NECC) in combination with one of the following:
   a) Cisplatin and etoposide
   b) Carboplatin and etoposide [6]

Hepatocellular Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. No disease progression on prior therapy with a PD-1 or PD-L1; AND
4. First-line treatment in combination with tremelimumab-actl or as a single agent for one of the following:
   a) Unresectable disease and is not a transplant candidate
   b) Liver-confined disease, inoperable by performance status, comorbidity, or with minimal or uncertain extrahepatic disease
   c) Metastatic disease or extensive liver tumor burden [7]

Non-Small Cell Lung Cancer (NSCLC)

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. No disease progression on prior therapy with a PD-1 or PD-L1; AND
4. Consolidation immunotherapy for unresectable stage II-III disease, performance status (PS) 0-1, and no disease progression after definitive concurrent chemoradiation; 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 with performance status 0-2 for one of the following combinations with tremelimumab-actl:
   a) Albumin-bound paclitaxel and carboplatin
   b) Pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology
   c) Gemcitabine, and either carboplatin or cisplatin for squamous cell histology; OR
6. Treatment for recurrent, advanced, or metastatic disease with performance status 0-1 and no contraindications to PD-1 or PD-L1 inhibitors in combination with tremelimumab-actl and one of the following:
   a) Albumin-bound paclitaxel and carboplatin
   b) Pemetrexed and either carboplatin or cisplatin for nonsquamous cell histology
   c) Gemcitabine and either carboplatin or cisplatin for squamous cell histology

   The above regimens listed under #6 for non-small cell lung cancer are used for the treatment indications 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 or subsequent therapy for BRAF V600E mutation positive tumors
   v. First-line or subsequent therapy for NTRK1/2/3 gene fusion positive tumors
   vi. First-line or subsequent therapy for MET exon 14 skipping mutation positive tumors
   vii. First-line or subsequent therapy for RET rearrangement positive tumors
   viii. First-line therapy for ERBB2 (HER2) mutation 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 for 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; OR

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, 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 (i.e., 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.

7. Continuation maintenance therapy as a single agent 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 performance status 0-2 who achieve a response or stable disease following first-line therapy with durvalumab, tremelimumab-actl plus chemotherapy; OR
8. 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 performance status 0-2 who achieve a response or stable disease following first line therapy with durvalumab, tremelimumab-actl, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology; OR
9. Continuation maintenance therapy as a single agent 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 in those with performance status 0-2 who achieve tumor response or stable disease following initial systemic therapy with durvalumab, tremelimumab-actl plus chemotherapy; OR
10. Continuation maintenance therapy in combination with pemetrexed 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 in those with performance status 0-2 who achieve tumor response or stable disease following initial systemic therapy with durvalumab, tremelimumab-actl, pemetrexed, and either carboplatin or cisplatin for nonsquamous cell histology

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, 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 (i.e., 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]

Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND
3. No disease progression on prior therapy with a PD-1 or PD-L1; AND
4. Preferred primary treatment in combination with etoposide and either carboplatin or cisplatin followed by single-agent maintenance for extensive stage disease in those with one of the following indications:
   a) Without localized symptomatic sites or brain metastases and good performance status (PS 0-2)

b) Without localized symptomatic sites or brain metastases and poor PS (3-4) due to small cell lung cancer
c) With localized symptomatic sites
d) With brain metastases

Note: Coverage of durvalumab 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

Durvalumab: References

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13. 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.

Durvalumab: 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
C24.1	Malignant neoplasm - ampullary
C24.9	Malignant Neoplasm of the biliary tract
C34.90	Malignant neoplasm of unspecified part of unspecified bronchus or lung
C53.0	Malignant neoplasm - cervical
J9173	Durvalumab (Imfinzi)

Durvalumab: Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	1/1/2024
2	Policy Review Dates:	7/28/2023
3	Policy Revision Dates:	
4	Department Owner:	Medical Affairs
5	NH Advisory Committee Approval Dates:	9/20/2023

6	Revision Changes:	