CLINICAL GUIDELINES FOR MEDICAL NECESSITY

MEDICAL POLICY

Larotrectinib (Vitrakvi®)

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NantHealth® | Eviti®

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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.

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.

Larotrectinib (Vitrakvi®)

Discussion

Larotrectinib is a targeted cancer therapy that inhibits the tropomyosin receptor kinases TRKA, TRKB, and TRKC, which are encoded by the genes NTRK1, NTRK2, and NTRK3, respectively. These kinases are involved in cell growth and survival. Larotrectinib is highly effective at low concentrations, with IC50 values between 5–11 nM. Chromosomal rearrangements can create in-frame fusions involving NTRK genes, leading to constitutively active TRK fusion proteins that act as oncogenic drivers in various tumors. Larotrectinib exhibits potent anti-tumor activity in cells with TRK activation resulting from gene fusions or overexpression; however, it has limited effectiveness against TRKA point mutations, such as the resistance-associated G595R variant.[1]

It inhibits these kinases by competing with ATP, preventing phosphorylation and subsequent activation of downstream signaling pathways. This inhibition leads to the suppression of tumor growth and proliferation in cancers harboring NTRK gene fusions.[2]

Larotrectinib demonstrated anti-tumor activity in cells with constitutive activation of TRK proteins resulting from gene fusions, deletion of a protein regulatory domain, or in cells with TRK protein overexpression. Larotrectinib had minimal activity in cell lines with point mutations in the TRKA kinase domain, including the clinically identified acquired resistance mutation, G595R.

Clinically significant adverse reactions include central nervous system effects, skeletal fractures, hepatotoxicity, and embryo-fetal toxicity. The most common adverse reactions were laboratory abnormalities such as increased AST (aspartate aminotransferase), increased ALT (alanine aminotransferase), anemia, hypoalbuminemia, increased alkaline phosphatase, leukopenia, lymphopenia, neutropenia, and hypocalcemia. Other common adverse reactions were musculoskeletal pain, fatigue, vomiting, cough, constipation, pyrexia (fever), diarrhea, nausea, abdominal pain, dizziness, and rash.

Larotrectinib is approved by the Food and Drug Administration (FDA) for solid tumors.[1] The National Comprehensive Cancer Network (NCCN) endorses larotrectinib for the following cancer types: ampullary adenocarcinoma, biliary tract, breast, central nervous system, cervical, colon, esophageal and esophagogastric junction, gastric, gastrointestinal stromal, head and neck, hepatocellular, histiocytic neoplasms, melanoma: cutaneous, non-small cell lung, neuroendocrine and adrenal tumors, occult primary, ovarian cancer, pancreatic, pediatric central nervous system, rectal, small bowel, soft tissue sarcoma, thyroid, uterine, vaginal, and vulvar.[3,4,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26,27,28]

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.[29]
- **National Comprehensive Cancer Network (NCCN)** - An alliance of more than 30 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.[30]

Policy

Coverage will be considered for FDA approved indications and for NCCN category 1, 2A, or 2B recommendations 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

For **NCCN** required criteria coverage:

3. First-line therapy as a single agent if NTRK gene-fusion positive for metastatic disease; OR
4. Single agent for disease progression if NTRK gene-fusion positive.[3]

Biliary Tract Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Gallbladder Cancer

For **NCCN** required criteria coverage:

3. Single agent as neoadjuvant systemic therapy for NTRK gene-fusion positive resectable locoregionally advanced disease that presents as one of the following:
   a) Incidental finding of a suspicious mass during surgery, where hepatobiliary surgery expertise is unavailable
   b) Incidental finding on pathologic review (cystic duct node positive)
   c) Mass on imaging
   d) Jaundice; OR
4. Primary treatment for unresectable or gross residual (R2) disease, or metastatic disease that is NTRK gene-fusion positive, as a single agent; OR
5. Subsequent treatment for progression on or after systemic treatment for unresectable or gross residual (R2) disease, or metastatic disease that is NTRK gene-fusion positive as a single agent

   Note: Larotrectinib should not be used if there was progression on prior NTRK inhibitor; OR

Intrahepatic Cholangiocarcinoma

For **NCCN** required criteria coverage:

6. Primary treatment as a single agent for unresectable or gross residual (R2) disease, or metastatic disease that is NTRK gene fusion positive; OR

7. Subsequent treatment as a single agent for progression on or after systemic treatment for unresectable or gross residual (R2) disease, or metastatic disease that is NTRK gene-fusion positive

   Note: Larotrectinib should not be used if there was progression on prior NTRK inhibitor; OR

Extrahepatic Cholangiocarcinoma

For **NCCN** required criteria coverage:

8. Primary treatment as a single agent for unresectable or gross residual (R2) disease, or metastatic disease that is NTRK gene-fusion positive; OR
9. Subsequent treatment as a single agent for progression on or after systemic treatment for unresectable or gross residual (R2) disease, or metastatic disease that is NTRK gene-fusion positive

   Note: Larotrectinib should not be used if there was progression on prior NTRK inhibitor.[4]

Breast Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Invasive Breast Cancer

For **NCCN** required criteria coverage:

3. Single agent therapy for recurrent unresectable (local or regional) or stage IV (M1) disease that has an NTRK gene-fusion without a known acquired resistance mutation and has no satisfactory alternative treatments, or that has progressed following treatment for one of the following:
   a) Third-line therapy and beyond for hormone receptor positive and human epidermal growth factor receptor 2 (HER2)-negative with visceral crisis or endocrine therapy refractory, or for triple negative breast cancer (TNBC)
   b) Fourth-line and beyond for HER2-positive disease; OR

Inflammatory Breast Cancer

For **NCCN** required criteria coverage:

4. Single agent therapy for patients with no response to preoperative systemic therapy, or recurrent unresectable (local or regional) or stage IV (M1) disease that has an NTRK gene fusion without a known acquired resistance mutation and has no satisfactory alternative treatments or that has progressed following treatment:
   a) Third-line therapy and beyond for hormone receptor positive and human epidermal growth factor receptor 2 (HER2)-negative with visceral crisis or endocrine therapy refractory, or for triple negative breast cancer (TNBC)
   b) Fourth-line and beyond for HER2-positive disease.[5]

Central Nervous System Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Circumscribed Glioma

For **NCCN** required criteria coverage:

3. Single-agent treatment for NTRK gene-fusion positive recurrent or progressive WHO grade 1 circumscribed glioma or WHO grade 2 pleomorphic xanthoastrocytoma (PXA), circumscribed glioma; OR

Glioblastoma

For **NCCN** required criteria coverage:

4. Recurrent or progressive NTRK gene-fusion positive disease as a single agent; OR

High Grade Glioma: Other

For **NCCN** required criteria coverage:

5. Recurrent or progressive NTRK gene-fusion positive disease as a single agent; OR

Limited Brain Metastases

For **NCCN** required criteria coverage:

6. Single-agent treatment for disease metastases in NTRK gene-fusion tumors for one of the following:
   a) Initial treatment in select cases (e.g., small asymptomatic brain metastases) for newly diagnosed or stable systemic disease or if reasonable systemic treatment options exist
   b) Recurrent brain metastases; OR

Extensive Brain Metastases

For **NCCN** required criteria coverage:

7. Single-agent treatment for disease metastases in NTRK gene-fusion tumors for one of the following:
   a) Primary treatment in select cases (e.g., small asymptomatic brain metastases)
   b) Recurrent disease with stable systemic disease or reasonable systemic treatment options.[6]

Cervical Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line or subsequent therapy as a single agent for NTRK gene-fusion positive tumors for one of the following:
   a) Locoregional recurrence
   b) Stage IVB or recurrence with distant metastases.[7]

Colon Cancer and Appendiceal Adenocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line and subsequent therapy (biomarker-driven) as a single agent, if not previously given, for progression of advanced or metastatic disease (proficient mismatch repair/microsatellite-stable (pMMR/MSS) or ineligible for or progressed on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [eg, TMB >50 mut/Mb]) (NTRK gene-fusion positive).[8]

Esophageal and Esophagogastric Junction Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Palliative therapy for patients with NTRK gene-fusion positive tumors who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic disease and Karnofsky performance score ≥60% or ECOG performance score ≤2 as first-line, second-line, or subsequent therapy as a single agent.[9]

Gastric Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Primary treatment as a single agent for patients with NTRK gene-fusion positive tumors who are medically fit for surgery but with surgically unresectable locoregional disease; OR
4. Palliative therapy for patients with NTRK gene-fusion positive tumors who are not surgical candidates or have unresectable locally advanced, recurrent, or metastatic adenocarcinoma (including peritoneal only metastatic disease, including positive cytology) and Karnofsky performance score ≥60% or ECOG performance score ≤2 as first-line, second-line or subsequent therapy as a single agent.[10]

Gastrointestinal Stromal Tumors

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Neoadjuvant therapy as a single agent to decrease surgical morbidity for NTRK gene-fusion positive GIST that are resectable with significant morbidity; OR
4. First-line therapy as a single agent for NTRK gene-fusion positive GIST with gross residual disease (R2 resection), unresectable primary disease, preoperative/intraoperative tumor rupture, or recurrent/metastatic disease, and as continued treatment for limited progression

   Note:
   1. Lifelong systemic therapy is recommended for TKI-sensitive GIST
   2. Clinical experience suggests that discontinuing TKI therapy, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.[11]

Head and Neck Cancers

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Salivary Gland Tumors

For **NCCN** required criteria coverage:

3. Single agent systemic therapy for NTRK gene-fusion positive recurrent disease for one of the following:
   a) Distant metastases in patients with a performance status (PS) of 0-3
   b) Unresectable locoregional recurrence or second primary with prior radiation therapy.[12]

Hepatocellular Carcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Subsequent-line systemic therapy as a single agent if progression on or after systemic therapy for NTRK gene-fusion positive tumors.[13]

Histiocytic Neoplasms

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Erdheim-Chester Disease

For **NCCN** required criteria coverage:

3. First-line or subsequent therapy for neurotrophic tyrosine kinase (NTRK) gene-fusion target as a single agent, for one of the following:
   a) Symptomatic disease
   b) Relapsed/refractory disease; OR

Langerhans Cell Histiocytosis

For **NCCN** required criteria coverage:

4. First-line or subsequent therapy for neurotrophic tyrosine kinase (NTRK) gene-fusion target as a single agent, useful in certain circumstances, for one of the following:
   a) Multisystem Langerhans Cell Histiocytosis (LCH) with symptomatic or impending organ dysfunction or critical organ involvement
   b) Single-system lung LCH
   c) Multifocal single-system bone disease not responsive to treatment with a bisphosphonate (useful in certain circumstances)
   d) CNS lesions
   e) Relapsed/refractory disease; OR

Rosai-Dorfman Disease

For **NCCN** required criteria coverage:

5. First-line or subsequent therapy for neurotrophic tyrosine kinase (NTRK) gene-fusion target as a single agent, for one of the following:
   a) Symptomatic unresectable (bulky/site of disease) unifocal disease
   b) Symptomatic multifocal disease
   c) Relapsed/refractory disease.[14]

Melanoma: Cutaneous

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent for metastatic or unresectable disease that is NTRK gene-fusion positive as second-line or subsequent therapy for disease progression, intolerance, or projected risk of progression with BRAF-targeted therapy.[15]

Non-Small Cell Lung Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single-agent therapy for recurrent, advanced, or metastatic disease in those with NTRK1/2/3 gene-fusion positive tumors for one of the following:

a) First-line therapy (if NTRK1/2/3 gene-fusion discovered prior to first-line systemic therapy)
b) Subsequent therapy following progression on first-line systemic therapy with a non-NTRK1/2/3-targeted regimen.[16]

Neuroendocrine and Adrenal Tumors

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Extrapulmonary Poorly Differentiated: Neuroendocrine Carcinoma/Large or Small Cell Carcinoma/Mixed Neuroendocrine-Non-Neuroendocrine Neoplasm

For **NCCN** required criteria coverage:

3. Subsequent therapy if progression on first-line therapy for locoregional unresectable or metastatic NTRK gene-fusion positive tumors without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity, and that have no satisfactory alternative treatments, or that have progressed following treatment.[17]

Occult Primary

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Single agent (in patients with NTRK gene-fusion positive tumors without a known acquired resistance mutation) in symptomatic patients with performance status (PS) 1-2 or asymptomatic patients with PS 0 and aggressive disease that is metastatic or where surgical resection is likely to result in severe morbidity, and that progressed following treatment or has no satisfactory alternative treatments for one of the following:
   a) Axillary involvement in those with a prostate or post-prostatectomy if clinically indicated
   b) Lung nodules or breast marker-negative pleural effusion
   c) Resectable liver disease
   d) Peritoneal mass or ascites with non-ovarian histology
   e) Retroperitoneal mass of non-germ cell histology in selected patients
   f) Unresectable liver disease or disseminated metastases; OR
4. Single agent (in patients with NTRK gene-fusion positive tumors without a known acquired resistance mutation) in symptomatic patients with performance status (PS) 1-2 or asymptomatic patients with PS 0 and aggressive disease for systemic therapy in patients with multiple lung nodules, pleural effusion, or disseminated metastases or where surgical resection is likely to result in severe morbidity, and that have no satisfactory alternative treatments or that have progressed following treatment.[18]

Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

1. At least 18 years of age; AND

2. Prescribed by or in consultation with an oncologist; AND

Carcinosarcoma (Malignant Mixed Müllerian Tumors)

For **NCCN** required criteria coverage:

3. Single-agent therapy disease persistence or recurrence in NTRK gene-fusion positive tumors for one of the following:
   a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
   b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
   c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
   d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)
   e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR

Clear Cell Carcinoma of the Ovary

For **NCCN** required criteria coverage:

4. Single-agent therapy for disease persistence or recurrence in NTRK gene-fusion positive tumors for one of the following:
   a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
   b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
   c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
   d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)
   e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR

Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

For **NCCN** required criteria coverage:

5. Single-agent therapy for disease persistence or recurrence in NTRK gene-fusion positive tumors for one of the following:
   a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
   b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
   c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
   d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)
   e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR

Grade 1 Endometrioid Carcinoma

For **NCCN** required criteria coverage:

6. Single-agent therapy for disease persistence or recurrence in NTRK gene-fusion positive tumors for one of the following:
   a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
   b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
   c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
   d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)
   e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR

Mucinous Neoplasms of the Ovary

For **NCCN** required criteria coverage:

7. Single-agent therapy for disease persistence or recurrence in NTRK gene-fusion positive tumors for one of the following:
   a) Immediate treatment for serially rising CA-125 in patients that previously received chemotherapy
   b) Progression on primary, maintenance, or recurrence therapy (platinum-resistant disease)
   c) Stable or persistent disease (if not on maintenance therapy) (platinum-resistant disease)
   d) Complete remission and relapse <6 months after completing chemotherapy (platinum-resistant disease)
   e) Radiographic and/or clinical relapse in patients with previous complete remission and relapse ≥6 months after completing prior chemotherapy (platinum-sensitive disease); OR

Low-Grade Serous Carcinoma

For **NCCN** required criteria coverage:

8. Single-agent therapy for platinum-sensitive or platinum-resistant recurrence in NTRK gene-fusion positive tumors.[19]

Pancreatic Adenocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. First-line therapy as a single agent if NTRK gene-fusion positive for one of the following:
   a) Locally advanced or metastatic disease if good performance status (defined as ECOG PS 0-1, with good biliary drainage and adequate nutritional intake)
   b) Locally advanced or metastatic disease if intermediate PS (ECOG 2)

   c) Metastatic disease with poor PS (ECOG 3); OR
4. Subsequent therapy as a single agent (if NTRK gene-fusion positive) for locally advanced or metastatic disease, and disease progression for one of the following:
   a) Good performance status (defined as ECOG PS 0-1, with good biliary drainage and adequate nutritional intake)
   b) Intermediate PS (ECOG 2)
   c) Poor PS (ECOG 3); OR
5. Single agent (if NTRK gene-fusion positive) if good performance status (ECOG PS 0-1), intermediate PS (ECOG 2), or poor PS (ECOG 3) for one of the following:
   a) Local recurrence in the pancreatic operative bed after resection
   b) Recurrent metastatic disease with or without local recurrence after resection

   Note: As an alternate systemic therapy not previously used.[20]

Pediatric Central Nervous System Cancers

1. Less than 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Diffuse High-Grade Gliomas

For **NCCN** required criteria coverage:

3. Adjuvant treatment for NTRK-fusion positive pediatric diffuse high-grade glioma for one of the following:
   a) Following standard brain radiation therapy (RT) with or without concurrent temozolomide in patients ≥3 years old
   b) In patients <3 years old

   Note: Except diffuse midline glioma, H3 K27-altered, or pontine location; OR

4. Recurrent or progressive disease for NTRK-fusion positive pediatric diffuse high-grade glioma

   Note: Except oligodendroglioma, IDH-mutant and 1p/19q co-deleted or astrocytoma IDH-mutant.[21]

Rectal Cancer

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line and subsequent therapy as a single agent, if not previously given, for progression of advanced or metastatic disease (NTRK gene-fusion positive) (proficient mismatch repair/microsatellite-stable [pMMR/MSS] or ineligible for or progressed on checkpoint inhibitor immunotherapy for deficient mismatch repair/microsatellite instability-

high [dMMR/MSI-H] or polymerase epsilon/delta [POLE/POLD1] mutation with ultra-hypermutated phenotype [e.g., TMB >50 mut/Mb]).[22]

Small Bowel Adenocarcinoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line and subsequent therapy as a single agent for advanced or metastatic disease that is NTRK gene-fusion positive (if not previously given).[23]

Soft Tissue Sarcoma

1. At least 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Epithelioid Hemangioendothelioma

For **NCCN** required criteria coverage:

3. Single-agent therapy for NTRK gene-fusion positive epithelioid hemangioendothelioma; OR

Extremity, Body Wall, Head or Neck

For **NCCN** required criteria coverage:

4. First-line advanced/metastatic therapy for NTRK gene-fusion positive sarcomas only (regardless of soft tissue sarcoma subtype) as a single agent for one of the following:
   a) Unresectable primary disease following primary treatment for stage II, III, or select stage IV (any T, N1, M0) resectable disease, but with unacceptable functional outcomes or unresectable primary disease
   b) Primary treatment for metastases of synchronous stage IV oligometastatic disease with limited tumor bulk that is amenable to local therapy
   c) Before metastasectomy, after metastasectomy, or in addition to stereotactic body radiation therapy (SBRT) for recurrent metastatic disease that is single-organ confined with limited tumor bulk amenable to local therapy
   d) In addition to regional node dissection as part of primary treatment of a primary sarcoma with synchronous regional nodal metastatic disease for select stage IV (any T, N1, M0) resectable disease or in addition to regional node dissection for recurrent metastatic disease with isolated regional disease or nodes
   e) Palliative systemic therapy for synchronous stage IV with disseminated metastases or recurrent metastatic disease with disseminated metastases

   Note:
   1. If atypical lipomatous tumor/well-differentiated liposarcoma (ALT/WDLPS) (extremity, abdominal wall, trunk): if the disease that was initially diagnosed as ALT/WDLPS shows evidence of dedifferentiation, treat as other soft tissue sarcomas.

2. Not intended for neoadjuvant or adjuvant therapy of nonmetastatic disease and not recommended for angiosarcoma or pleomorphic rhabdomyosarcoma; OR

Retroperitoneal or Intra-Abdominal

For **NCCN** required criteria coverage:

5. First-line advanced/metastatic therapy for NTRK gene-fusion positive sarcomas only (regardless of soft tissue sarcoma subtype) as a single agent for one of the following:
   a) Residual disease (R2 resection)
   b) Unresectable localized disease (primary or recurrent)
   c) Combination with local therapies (including metastasectomy, SBRT, ablation, embolization) for stage IV disease with single organ and limited tumor bulk that are amenable to local therapy
   d) Palliative treatment of stage IV disease with disseminated metastases; OR
6. As alternative systemic single-agent therapy for NTRK gene-fusion positive sarcomas only (regardless of soft tissue sarcoma subtype) for unresectable or progressive disease after initial therapy for unresectable localized disease

Note:
1. Treat well-differentiated liposarcoma (WDLPS) (retroperitoneum, paratesticular) with or without evidence of de-differentiation as other soft tissue sarcomas
2. Not intended for neoadjuvant or adjuvant therapy of nonmetastatic disease and not recommended for angiosarcoma or pleomorphic rhabdomyosarcoma.[24]

Solid Tumors

1. Adult or pediatric patients; AND
2. Prescribed by or in consultation with an oncologist; AND

For **FDA** required criteria coverage:

3. Neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation; OR
4. Metastatic or where surgical resection is likely to result in severe morbidity; OR
5. No satisfactory alternative treatments have been found or have progressed following treatment.[1]

Thyroid Carcinoma

1. Greater than 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Anaplastic Carcinoma

For **NCCN** required criteria coverage:

3. For NTRK gene-fusion positive tumors, used as a single agent therapy for one of the following:

a) Molecularly targeted neoadjuvant therapy for borderline resectable stage IVA or IVB (locoregional) disease
b) Aggressive first-line therapy for stage IVC metastatic disease
c) Second-line therapy for stage IVC metastatic disease; OR

Follicular Carcinoma

For **NCCN** required criteria coverage:

4. For NTRK gene-fusion positive tumors, consider treatment of progressive and/or symptomatic disease for one of the following:
   a) Unresectable locoregional recurrent or persistent radioactive iodine (RAI)-refractory disease
   b) Distant metastatic RAI-refractory disease; OR

Oncocytic Carcinoma

For **NCCN** required criteria coverage:

5. For NTRK gene-fusion positive tumors, consider for treatment of progressive and/or symptomatic disease for one of the following:
   a) Unresectable locoregional recurrent or persistent disease
   b) Distant metastatic disease; OR

Papillary Carcinoma

For **NCCN** required criteria coverage:

6. For NTRK gene fusion-positive tumors, consider treatment for progressive and/or symptomatic disease for one of the following:
   a) Unresectable locoregional recurrent or persistent radioactive iodine (RAI)-refractory disease
   b) Distant metastatic RAI-refractory disease.[25]

Uterine Neoplasms

1. Greater than 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

Endometrial Carcinoma

For **NCCN** required criteria coverage:

3. Second-line or subsequent therapy as a single agent for recurrent disease that is NTRK gene- fusion positive (if not previously used) for one of the following:
   a) Considered for isolated metastases
   b) Disseminated metastases with or without sequential palliative external beam radiation therapy (EBRT)
   c) Sequential EBRT and with or without brachytherapy for locoregional recurrence in patients with no prior RT to site of recurrence, or previous vaginal brachytherapy only

d) After surgical exploration, with sequential EBRT for locoregional recurrence in patients with disease confined to the vagina or paravaginal soft tissue, or in pelvic or para-aortic lymph nodes
e) After surgical exploration, with or without sequential EBRT for locoregional recurrence in patients with upper abdominal or peritoneal disease
f) With or without sequential palliative EBRT or brachytherapy for locoregional recurrence in patients who have received prior EBRT to the site of recurrence; OR

Uterine Sarcoma

For **NCCN** required criteria coverage:

4. First-line therapy for advanced, recurrent/metastatic, or inoperable disease (or second-line or subsequent therapy as clinically appropriate if not used previously) as a single agent for NTRK gene-fusion positive tumors for one of the following:
   a) Primary treatment of known or suspected extrauterine disease, diagnosed by biopsy or myomectomy
   b) Primary treatment of disease that is not suitable for primary surgery (disease is not amenable to resection or patient is not suitable for surgery based on comorbidities)
   c) Additional therapy following total hysterectomy with bilateral salpingo-oophorectomy (TH + BSO) for stage II-IV adenosarcoma with sarcomatous overgrowth (recommended for residual measurable disease)
   d) Additional therapy following TH ± BSO for stage II-III high-grade endometrial stromal sarcoma (ESS), undifferentiated uterine sarcoma (UUS), leiomyosarcoma (LMS), or other sarcomas
   e) Additional therapy following TH ± BSO for stage IV high-grade ESS, UUS, LMS, or other sarcomas
   f) Preoperatively or postoperatively for recurrent disease with resectable isolated metastases
   g) Recurrent disease with unresectable isolated metastases or disseminated disease
   h) Radiologically isolated vaginal/pelvic recurrence if no prior radiation therapy (RT), given in combination with RT
   i) Radiologically isolated vaginal/pelvic recurrence if prior RT, given with or without RT.[26]

Vaginal Cancer

1. Greater than 18 years of age; AND
2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line or subsequent therapy as a single agent for NTRK gene-fusion positive tumors for one of the following:
   a) Locoregional recurrence
   b) Stage IVB or recurrent distant metastases.[27]

Vulvar Cancer

1. Greater than 18 years of age; AND

2. Prescribed by or in consultation with an oncologist; AND

For **NCCN** required criteria coverage:

3. Second-line or subsequent therapy for advanced or recurrent/metastatic disease as a single agent for NTRK gene-fusion positive tumors.[28]

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

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
C06.9	Malignant neoplasm of mouth, unspecified
C15.9	Malignant neoplasm of esophagus, unspecified
C16.9	Malignant neoplasm of stomach, unspecified
C17.0	Malignant neoplasm of duodenum
C20	Malignant neoplasm of rectum
C22.1	Intrahepatic bile duct carcinoma
C23	Malignant neoplasm of gallbladder
C24.0	Malignant neoplasm of extrahepatic bile duct
C24.1	Malignant neoplasm of ampulla of Vater
C25	Malignant neoplasm of pancreas
C43	Malignant melanoma of skin
C47.0	Malignant neoplasm of peripheral nerves of head, face and neck

C47.4	Malignant neoplasm of peripheral nerves of abdomen
C48.0	Malignant neoplasm of retroperitoneum
C49.A	Gastrointestinal stromal tumor
C50.0	Malignant neoplasm of nipple and areola
C52	Malignant neoplasm of vagina
C53	Malignant neoplasm of cervix uteri
C54.0	Malignant neoplasm of isthmus uteri
C56	Malignant neoplasm of ovary
C57.00	Malignant neoplasm of unspecified fallopian tube
C7A.8	Other malignant neuroendocrine tumors
C71.0	Malignant neoplasm of cerebrum, except lobes and ventricles
C79.31	Secondary malignant neoplasm of brain
C80.0	Disseminated malignant neoplasm, unspecified
C96.0	Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis
J8999	Prescription drug, oral, chemotherapeutic, not otherwise specified

Revision and Review History

No.	Description	Date(s)
1	Original Effective Date:	8/28/2025

2	Policy Annual Review Dates:	
3	Department Owner:	Medical Affairs
4	NH Advisory Committee Approval Dates:	8/28/2025
5	Revision Changes:	

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