Taipei Veterans General Hospital

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Sample Information

Patient Name: 邱美惠
Gender: Female
ID No.: J220743436
History No.: 46704534
Age: 52

Ordering Doctor: DOC1885G 楊慕華
Ordering REQ.: D5NH1E6
Signing in Date: 2021/01/27

Path No.: S110-98127
MP No.: F21007
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-90132A
Percentage of tumor cells: 80%
Note:

Sample Cancer Type: Head and Neck Cancer

Table of Contents

Report Highlights

1 Relevant Biomarkers
3 Therapies Available
10 Clinical Trials

Relevant Head and Neck Cancer Variants

Gene	Finding
ERBB2	Not detected
NTRK1	Not detected
NTRK2	Not detected
NTRK3	***ETV6-NTRK3 fusion***

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).The content of this report has not been evaluated or approved by the FDA or other regulatory agencies.

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*ETV6-NTRK3 fusion* ETS variant 6 - neurotrophic receptor tyrosine kinase 3	**entrectinib** [1, 2] **larotrectinib** [1]	entrectinib larotrectinib TRK inhibitor	10

Public data sources included in relevant therapies: FDA1, NCCN, **EMA**2, ESMO
Tier Reference: Li et al. *Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer: A Joint Consensus Recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists.* J Mol Diagn. 2017 Jan;19(1):4-23.

Variants (Exclude variant in Taiwan BioBank with >1% allele frequency)

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
ETV6-NTRK3	ETV6-NTRK3.E4N15.COSF823.1	chr12:12006495 - chr15:88483984	498
ETV6-NTRK3	ETV6-NTRK3.E5N15.COSF571.1	chr12:12022903 - chr15:88483984	131410

Biomarker Descriptions

ETV6 (ETS variant 6)

Background: The ETV6 gene encodes the E twenty-six (ETS) variant 1 transcription factor. ETV6 contains an N-terminal pointed (PNT) domain responsible for protein-protein interactions and a C-terminal ETS domain involved in DNA binding[1]. ETV6 plays a critical role in embryonic development as well as hematopoiesis and is the target of chromosomal rearrangement and missense mutations in hematological malignancies as well as solid tumors[2,3]. Hereditary mutations in ETV6 are associated with a predisposition to hematological cancers, including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and myelodysplastic syndromes (MDS)[4,5,6].

Alterations and prevalence: ETV6 translocations are prevalent in hematological malignancies and have been observed with numerous fusion partners[7]. The most recurrent translocation is t(12;21)(q34;q11) which results in ETV6-RUNX1 fusion and is observed in 20-25% childhood acute lymphoblastic leukemia (ALL)[7,8,9]. ETV6-RUNX1 fusions are also observed in adult ALL (2%)[8,9]. The t(5;12)(q33;p13) translocation which results in the ETV6-PDGFRB fusion is recurrent in chronic myelomonocytic leukemia (CMML)[7,10]. Other ETV6 fusions including ETV6-PDGFRA, ETV6-NTRK2, ETV6-NTRK3, and ETV6-ABL1 are reported in hematological malignancies as well as solid tumors[3,7,11]. ETV6 fusions involving a receptor tyrosine kinase (RTK) fusion partner retains the ETV6 PNT domain and the tyrosine kinase domain of the RTK, leading to constitutive kinase activation[7,11]. Mutations in ETV6 are primarily missense, nonsense, or frameshift and are observed in about 1-5% of select myeloid malignancies and solid tumors, including chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), diffuse large B-cell lymphoma (DLBCL), MDS, AML, ALL, melanoma, lung, bladder, stomach, colorectal, and uterine cancers[1,12,13]. ETV6 mutations occur in the PNT and ETS domain of ETV6 and may impair ETV6 oligomerization or DNA-binding, respectively[1].

Potential relevance: ETV6-NTRK3 fusions are used as an ancillary diagnostic marker in congenital/infantile fibrosarcoma[14]. Nonsense or frameshift mutations in ETV6 are independently associated with poor prognosis in MDS[6]. However, ETV6-RUNX1 fusions are associated with favorable outcomes in ALL and good risk in B-cell ALL (B-ALL)[9]. ETV6 fusions that partner with a RTKs demonstrate response to various tyrosine kinase inhibitors such as imatinib, nilotinib, and entrectinib. Specifically, individual case reports of an ETV6-PDGFRA fusion chronic eosinophilic leukemia patient and an ETV6-PDGFRB fusion CMML patient treated with imatinib demonstrated complete cytogenetic response (CCyR) and complete hematological responses, respectively[15,16]. Additionally, an ETV6-ABL1 fusion Ph-negative CML patient treated with nilotinib demonstrated CCyR and major molecular response (MMR) at 22 months from diagnosis[17]. In another case report, an ETV6-NTRK3 fusion mammary analogue secretory carcinoma (MASC) patient demonstrated partial response to entrectinib with 89% reduction in tumor burden[18].

NTRK3 (neurotrophic receptor tyrosine kinase 3)

Background: The NTRK genes encode a family of neurotrophic receptor tyrosine kinases that function as receptors for nerve growth factors. NTRKs are activated by different neurotrophins and are important for the development of the nervous system[19]. The NTRK1,2,3 proteins are also known as tropomyosin related kinases (TrkA,B,C) because NTRK1 was originally discovered as part of a chimeric fusion gene with tropomyosin-3 isolated from a human colon carcinoma cell line[20]. NTRKs are the target of recurrent chromosomal

Biomarker Descriptions (continued)

rearrangements that generate fusion proteins containing the intact tyrosine kinase domain combined with numerous fusion partner genes[21,22]. NTRK fusion kinases are constitutively active and lead to increased RAS/RAF/MEK/ERK, PI3K/AKT/MTOR, or PLCγ/PKC pathway signaling and can promote cell growth and proliferation[21,23].

Alterations and prevalence: NTRK fusions are infrequently observed in diverse cancer types including glioma, glioblastoma, lung adenocarcinoma, colorectal carcinoma, thyroid cancer, and sarcoma[13,21,24,25,26]. In certain cancer subtypes, including infantile fibrosarcoma, papillary thyroid carcinoma, and secretory carcinoma of the breast or salivary gland, NTRK fusions are more prevalent[21,27,28,29].

Potential relevance: The first-generation selective tropomyosin receptor kinase (TRK) inhibitor, larotrectinib[30], is approved (2018) for the treatment of patients with any solid tumors harboring NTRK gene fusions and is the first approved small molecule inhibitor with tissue agnostic indication. Entrectinib[31] is another first-generation TRK inhibitor approved (2019) for NTRK fusion-positive solid tumors as well as ROS1-positive non-small cell lung cancer (NSCLC). However, acquired resistance to first-generation NTRK inhibition is often mediated by the acquisition of solvent-front and gatekeeper mutations in the kinase domain[32]. Consequently, the second generation TRK inhibitor, repotrectinib[33], was granted fast-track designation by the FDA (2020) for the treatment of patients with advanced solid tumors and an NTRK gene fusion that have progressed following treatment with at least one prior line of chemotherapy and prior TRK inhibitor treatment.

Relevant Therapy Summary

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types ✖ No evidence

ETV6-NTRK3 fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
entrectinib	●	◑	●	✖	● (II)
larotrectinib	●	◑	✖	✖	● (II)
TRK inhibitor	✖	✖	✖	○	✖
cabozantinib	✖	✖	✖	✖	● (II)
temsirolimus	✖	✖	✖	✖	● (II)
repotrectinib	✖	✖	✖	✖	● (I/II)

* Most advanced phase (IV, III, II/III, II, I/II, I) is shown and multiple clinical trials may be available.

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

Relevant Therapy Details

Current FDA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

FDA information is current as of 2020-11-18. For the most up-to-date information, search www.fda.gov.

ETV6-NTRK3 fusion

● entrectinib

Cancer type: Solid Tumor **Label as of:** 2019-08-15 **Variant class:** NTRK fusion

Indications and usage:

ROZLYTREK® is a kinase inhibitor indicated for the treatment of:

- Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive.
- Adult and pediatric patients 12 years of age and older with solid tumors that:
  - have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation,
  - are metastatic or where surgical resection is likely to result in severe morbidity, and
  - have progressed following treatment or have no satisfactory alternative therapy

This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212726s000lbl.pdf

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● larotrectinib

Cancer type: Solid Tumor **Label as of:** 2018-11-26 **Variant class:** NTRK fusion

Indications and usage:

VITRAKVI® is a kinase inhibitor indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment.

This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210861s000lbl.pdf

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Current NCCN Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

NCCN information is current as of 2020-11-02. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

ETV6-NTRK3 fusion

● entrectinib

Cancer type: Solid Tumor **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Tumor agnostic; Brain metastases; See the appropriate NCCN treatment guidelines for systemic therapy recommendations for newly diagnosed brain metastases (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2020]

● entrectinib

Cancer type: Head and Neck Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Unresectable, or Metastatic Salivary Gland Tumors; PS 0-3 (Not Specified) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2020]

● larotrectinib

Cancer type: Solid Tumor **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Tumor agnostic; Brain metastases; See the appropriate NCCN treatment guidelines for systemic therapy recommendations for newly diagnosed brain metastases (Not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 3.2020]

● larotrectinib

Cancer type: Head and Neck Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent, Unresectable, or Metastatic Salivary Gland Tumors; PS 0-3 (Not Specified) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2020]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

ETV6-NTRK3 fusion (continued)

entrectinib

Cancer type: Breast Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent or Stage IV Invasive Breast Cancer (Not specified) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 6.2020]

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entrectinib

Cancer type: Colorectal Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic Colorectal Cancer (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2020]

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entrectinib

Cancer type: Melanoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy (Second-line or subsequent therapy) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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entrectinib

Cancer type: Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Locally Advanced, Recurrent or Metastatic Disease; Local therapy is not indicated (Second-line or subsequent therapy) (Other recommended regimen)

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 4.2020]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

ETV6-NTRK3 fusion (continued)

entrectinib

Cancer type: Gastric Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Locally Advanced, Recurrent or Metastatic Disease; Local therapy is not indicated (Second-line or subsequent therapy) (Other recommended regimen)

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 3.2020]

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entrectinib

Cancer type: Gastrointestinal Stromal Tumor **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Gastrointestinal Stromal Tumor; Unresectable with significant morbidity; Disease progression (Subsequent therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Gastrointestinal Stromal Tumor [Version 1.2021]

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entrectinib

Cancer type: Cholangiocarcinoma, Liver Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Gallbladder Cancer, Intra/Extrahepatic Cholangiocarcinoma; Unresectable or metastatic disease (Primary treatment) (Useful in Certain Circumstances)
- Gallbladder Cancer, Intra/Extrahepatic Cholangiocarcinoma; Disease progression; Dependent on clinical factors including previous treatment regimen/agent and extent of liver dysfunction (Subsequent therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2020]

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entrectinib

Cancer type: Liver Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Hepatocellular Carcinoma (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2020]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

ETV6-NTRK3 fusion (continued)

entrectinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Discovered prior to first-line systemic therapy (First-line therapy) (Preferred)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Discovered during first-line systemic therapy or disease progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2020]

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entrectinib

Cancer type: Ovarian Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Cancer; Platinum-Sensitive or Resistant (Recurrence therapy) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2020]

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entrectinib

Cancer type: Colorectal Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic Colorectal Cancer (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 6.2020]

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entrectinib

Cancer type: Soft Tissue Sarcoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Soft Tissue Sarcoma Subtypes with Non-Specific Histologies, appropriate General Soft Tissue Sarcoma or Pleomorphic Rhabdomyosarcoma; Advanced/Metastatic disease; Not intended for adjuvant therapy of nonmetastatic disease (First-line therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2021]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

ETV6-NTRK3 fusion (continued)

entrectinib

Cancer type: Thyroid Gland Anaplastic Carcinoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Thyroid Gland Anaplastic Carcinoma; Metastatic (Not specified) (Preferred)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2020]

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entrectinib

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; Unresectable locoregional recurrent/persistent disease not amenable to RAI therapy (Not specified)
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; CNS or soft tissue or bone metastases not amenable to RAI therapy (Not specified)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2020]

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larotrectinib

Cancer type: Breast Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Recurrent or Stage IV Invasive Breast Cancer (Not specified) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 6.2020]

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larotrectinib

Cancer type: Colorectal Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic Colorectal Cancer (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 4.2020]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

ETV6-NTRK3 fusion (continued)

larotrectinib

Cancer type: Melanoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic or Unresectable Cutaneous Melanoma; Progression or maximum clinical benefit from BRAF targeted therapy (Second-line or subsequent therapy) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 4.2020]

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larotrectinib

Cancer type: Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Locally Advanced, Recurrent or Metastatic Disease; Local therapy is not indicated (Second-line or subsequent therapy) (Other recommended regimen)

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 4.2020]

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larotrectinib

Cancer type: Gastric Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable Locally Advanced, Recurrent or Metastatic Disease; Local therapy is not indicated (Second-line or subsequent therapy) (Other recommended regimen)

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 3.2020]

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larotrectinib

Cancer type: Gastrointestinal Stromal Tumor **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Gastrointestinal Stromal Tumor; Unresectable with significant morbidity; Disease progression (Subsequent therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Gastrointestinal Stromal Tumor [Version 1.2021]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

ETV6-NTRK3 fusion (continued)

larotrectinib

Cancer type: Cholangiocarcinoma, Liver Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Gallbladder Cancer, Intra/Extrahepatic Cholangiocarcinoma; Unresectable or metastatic disease (Primary treatment) (Useful in Certain Circumstances)
- Gallbladder Cancer, Intra/Extrahepatic Cholangiocarcinoma; Disease progression; Dependent on clinical factors including previous treatment regimen/agent and extent of liver dysfunction (Subsequent therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2020]

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larotrectinib

Cancer type: Liver Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Hepatocellular Carcinoma (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 5.2020]

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larotrectinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Discovered prior to first-line systemic therapy (First-line therapy) (Preferred)
- Adenocarcinoma, Large Cell, Non-Small Cell Lung Cancer (NOS), Squamous Cell Carcinoma; Advanced or metastatic disease; Discovered during first-line systemic therapy or disease progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 8.2020]

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larotrectinib

Cancer type: Ovarian Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial Ovarian Cancer, Fallopian Tube Cancer, Primary Peritoneal Cancer; Platinum-Sensitive or Resistant (Recurrence therapy) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Ovarian Cancer [Version 1.2020]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

ETV6-NTRK3 fusion (continued)

larotrectinib

Cancer type: Pancreatic Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic Pancreatic Adenocarcinoma; Poor performance status (First-line therapy) (Useful in Certain Circumstances)
- Locally Advanced, Metastatic, or Recurrent Pancreatic Adenocarcinoma; Good or Poor performance status (Subsequent therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 1.2021]

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larotrectinib

Cancer type: Colorectal Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Metastatic Colorectal Cancer (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Rectal Cancer [Version 6.2020]

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larotrectinib

Cancer type: Soft Tissue Sarcoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Soft Tissue Sarcoma Subtypes with Non-Specific Histologies, appropriate for General Soft Tissue Sarcoma; Advanced/ Metastatic disease; Not intended for preoperative or adjuvant therapy of nonmetastatic disease; Not recommended for Angiosarcoma or Pleomorphic Rhabdomyosarcoma (First-line therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2021]

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larotrectinib

Cancer type: Thyroid Gland Anaplastic Carcinoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Thyroid Gland Anaplastic Carcinoma; Metastatic (Not specified) (Preferred)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2020]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

ETV6-NTRK3 fusion (continued)

larotrectinib

Cancer type: Thyroid Gland Follicular Carcinoma, Thyroid Gland Hurthle Cell Carcinoma, Thyroid Gland Papillary Carcinoma

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; Unresectable locoregional recurrent/persistent disease not amenable to RAI therapy (Not specified)
- Thyroid Gland Papillary, Follicular, Hurthle Cell Carcinoma; CNS or soft tissue or bone metastases not amenable to RAI therapy (Not specified)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 2.2020]

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entrectinib

Cancer type: Cervical Cancer

Variant class: NTRK fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Recurrent or Metastatic Cervical Cancer (Second-line therapy) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2021]

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entrectinib

Cancer type: Pancreatic Cancer

Variant class: NTRK fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Metastatic Pancreatic Adenocarcinoma; Poor performance status (First-line therapy) (Useful in Certain Circumstances)
- Locally Advanced, Metastatic, or Recurrent Pancreatic Adenocarcinoma; Good or Poor performance status (Subsequent therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 1.2021]

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entrectinib

Cancer type: Endometrial Cancer

Variant class: NTRK fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Advanced or Recurrent Endometrial Carcinoma (Not specified) (Useful in Certain Circumstances)
- Recurrent or Metastatic Uterine Sarcoma; Progression on prior cytotoxic chemotherapy (Second-line therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2021]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

ETV6-NTRK3 fusion (continued)

larotrectinib

Cancer type: Cervical Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Recurrent or Metastatic Cervical Cancer (Second-line therapy) (Useful in certain circumstances)

Reference: NCCN Guidelines® - NCCN-Cervical Cancer [Version 1.2021]

larotrectinib

Cancer type: Endometrial Cancer **Variant class:** NTRK fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Advanced or Recurrent Endometrial Carcinoma (Not specified) (Useful in Certain Circumstances)
- Recurrent or Metastatic Uterine Sarcoma; Progression on prior cytotoxic chemotherapy (Second-line therapy) (Useful in Certain Circumstances)

Reference: NCCN Guidelines® - NCCN-Uterine Neoplasms [Version 1.2021]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

Current EMA Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

EMA information is current as of 2020-11-18. For the most up-to-date information, search www.ema.europa.eu/ema.

ETV6-NTRK3 fusion

● entrectinib

Cancer type: Solid Tumor **Label as of:** 2020-10-27 **Variant class:** NTRK fusion

Reference:

https://www.ema.europa.eu/en/documents/product-information/rozlytrek-epar-product-information_en.pdf

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

Current ESMO Information

● In this cancer type ○ In other cancer type ◑ In this cancer type and other cancer types

ESMO information is current as of 2020-11-02. For the most up-to-date information, search www.esmo.org.

ETV6-NTRK3 fusion

○ TRK inhibitor

Cancer type: Breast Cancer **Variant class:** NTRK fusion

ESMO Level of Evidence/Grade of Recommendation: I / B

Population segment (Line of therapy):
- Advanced Breast Cancer (Not specified)

Reference: ESMO Clinical Practice Guidelines - ESMO-ESO-ESMO Advanced Breast Cancer [Annals of Oncology (2020), doi: https://doi.org/10.1016/j.annonc.2020.09.010 (ABC 5)]

Clinical Trials Summary

ETV6-NTRK3 fusion

NCT ID	Title	Phase
NCT02576431	A Phase II Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects With NTRK Fusion-positive Tumors	II
NCT02568267	An Open-Label, Multicenter, Global Phase II Basket Study of Entrectinib for the Treatment of Patients With Locally Advanced or Metastatic Solid Tumors That Harbor NTRK1/2/3, ROS1, or ALK Gene Rearrangements Studies of Tumor Alterations Responsive to Targeting Receptor Kinases (STARTRK-2)	II
NCT02465060	Molecular Analysis for Therapy Choice (MATCH).	II
NCT03155620	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) Screening Protocol	II
NCT03213704	NCI-COG Pediatric MATCH (Molecular Analysis for Therapy Choice) - Phase II Subprotocol of LOXO-101 (Larotrectinib) in Patients With Tumors Harboring Actionable NTRK Fusions	II
NCT03834961	Larotrectinib (LOXO-101, NSC# 788607) for Previously Untreated TRK Fusion Pediatric Solid Tumors and TRK Fusion Relapsed Pediatric Acute Leukemias	II
NCT02637687	A Phase I/II Study of the Oral TRK Inhibitor LOXO-101 in Pediatric Patients With Advanced Solid or Primary Central Nervous System Tumors	I/II
NCT03093116	A Phase I/II, Open-Label, Multi-Center, First-in-Human Study of the Safety, Tolerability, Pharmacokinetics, and Anti-Tumor Activity of TPX-0005 in Patients With Advanced Solid Tumors Harboring ALK, ROS1, or NTRK1-3 Rearrangements (TRIDENT-1)	I/II
NCT04116541	MegaMOST - A Multicenter, Open-label, Biology Driven, Phase II Study Evaluating the Activity of Anti-cancer Treatments Targeting Tumor Molecular Alterations /Characteristics in Advanced / Metastatic Tumors.	II
NCT03297606	Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR): A Phase II Basket Trial	II

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Alerts Informed By Public Data Sources

Current NCCN Information

Contraindicated Not recommended Resistance

NCCN information is current as of 2020-11-02. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

ETV6-NTRK3 fusion

larotrectinib

Cancer type: Angiosarcoma **Variant class:** NTRK fusion

Summary:

NCCN Guidelines® include the following supporting statement(s):

- "Not recommended for angiosarcoma or pleomorphic rhabdomyosarcoma."

Reference: NCCN Guidelines® - NCCN-Soft Tissue Sarcoma [Version 1.2021]

Disclaimer: The data presented here is from a curated knowledgebase of publicly available information, but may not be exhaustive. The data version is 2020.12(007).

Signatures

Testing Personnel:  2021.01.28 15:07:38 +08'00'

Laboratory Supervisor:  2021.01.28 15:07:52 +08'00'

Pathologist:  2021.01.28 15:08:06 +08'00'

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