Taipei Veterans General Hospital

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Sample Information

Patient Name: 吳福壹
Gender: Male
ID No.: G121276065
History No.: 32217917
Age: 46

Ordering Doctor: DOC8727C 林彥廷
Ordering REQ.: 0BFVACZ
Signing in Date: 2021/05/05

Path No.: S110-98764
MP No.: F21040
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-15770A+B
Percentage of tumor cells: 30%
Note:

Sample Cancer Type: Non-Small Cell Lung Cancer

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Relevant Non-Small Cell Lung Cancer Variants

Gene	Finding	Gene	Finding
ALK	Not detected	NTRK1	***TPM3-NTRK1 fusion***
BRAF	Not detected	NTRK2	Not detected
EGFR	Not detected	NTRK3	Not detected
ERBB2	Not detected	RET	Not detected
KRAS	Not detected	ROS1	Not detected
MET	Not detected		

Relevant Biomarkers

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
IA	*TPM3-NTRK1 fusion* tropomyosin 3 - neurotrophic receptor tyrosine kinase 1	**entrectinib** [1, 2] **larotrectinib** [1]	entrectinib larotrectinib TRK inhibitor	19

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
TPM3-NTRK1	TPM3-NTRK1.T7N12	chr1:154142876 - chr1:156845312	11071

Biomarker Descriptions

NTRK1 (neurotrophic receptor tyrosine kinase 1)

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[1]. 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[2]. NTRKs are the target of recurrent chromosomal rearrangements that generate fusion proteins containing the intact tyrosine kinase domain combined with numerous fusion partner genes[3,4]. 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[3,5].

Alterations and prevalence: NTRK fusions are infrequently observed in diverse cancer types including glioma, glioblastoma, lung adenocarcinoma, colorectal carcinoma, thyroid cancer, and sarcoma[3,6,7,8,9]. In certain cancer subtypes, including infantile fibrosarcoma, papillary thyroid carcinoma, and secretory carcinoma of the breast or salivary gland, NTRK fusions are more prevalent[3,10,11,12].

Potential relevance: The first-generation selective tropomyosin receptor kinase (TRK) inhibitor, larotrectinib[13], 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[14] 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[15]. Consequently, the second generation TRK inhibitor, repotrectinib[16], 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

TPM3-NTRK1 fusion

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
entrectinib	●	◑	●	✖	● (II)
larotrectinib	●	◑	✖	✖	● (II)

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

Relevant Therapy Summary (continued)

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

TPM3-NTRK1 fusion (continued)

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
TRK inhibitor	✖	✖	✖	○	✖
cabozantinib	✖	✖	✖	✖	● (II)
ensartinib	✖	✖	✖	✖	● (II)
ICP-723	✖	✖	✖	✖	● (I/II)
repotrectinib	✖	✖	✖	✖	● (I/II)
selitrectinib	✖	✖	✖	✖	● (I/II)
SIM1803-1A	✖	✖	✖	✖	● (I)
VMD-928	✖	✖	✖	✖	● (I)

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

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 2021-04-14. For the most up-to-date information, search www.fda.gov.

TPM3-NTRK1 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

TPM3-NTRK1 fusion (continued)

larotrectinib

Cancer type: Solid Tumor **Label as of:** 2021-03-25 **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.

Select patients for therapy based on an FDA-approved test.

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/2021/210861s006lbl.pdf

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 2021-04-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

TPM3-NTRK1 fusion

● entrectinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** NTRK1 fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2021]

● larotrectinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** NTRK1 fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (First-line therapy); Preferred intervention
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic (Subsequent therapy)
- Adenocarcinoma, Large Cell, Squamous Cell, Not otherwise specified (NOS); Advanced, Metastatic, Progression (Subsequent therapy)

Reference: NCCN Guidelines® - NCCN-Non-Small Cell Lung Cancer [Version 4.2021]

● entrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 4.2020]

TPM3-NTRK1 fusion (continued)

larotrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Brain Metastases (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 4.2020]

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entrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IV; Recurrent, Invasive, Unresectable, Local (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 3.2021]

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entrectinib

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 2.2021]

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entrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Cutaneous; Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

TPM3-NTRK1 fusion (continued)

entrectinib

Cancer type: Esophageal Cancer, Gastroesophageal Junction Adenocarcinoma

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma, Squamous Cell; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 1.2021]

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entrectinib

Cancer type: Gastric Cancer

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2021]

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entrectinib

Cancer type: Gastrointestinal Stromal Tumor

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Progression (Subsequent therapy); Useful in certain circumstances

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

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entrectinib

Cancer type: Head and Neck Cancer

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2021]

TPM3-NTRK1 fusion (continued)

entrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Gallbladder Cancer, Intrahepatic, Extrahepatic; Unresectable, Metastatic (First-line therapy); Useful in certain circumstances
- Gallbladder Cancer, Intrahepatic, Extrahepatic; Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 1.2021]

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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 1.2021]

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entrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Useful in certain circumstances

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

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entrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma; Locally Advanced, Metastatic, Recurrent (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2021]

TPM3-NTRK1 fusion (continued)

entrectinib

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

NCCN Recommendation category: 2A

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

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

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entrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unspecified histology; Advanced, Metastatic (First-line therapy); Useful in certain circumstances

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

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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):
- Locally Recurrent, Advanced, Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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entrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVC; Metastatic (Line of therapy not specified); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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larotrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IV; Recurrent, Invasive, Unresectable, Local (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 3.2021]

TPM3-NTRK1 fusion (continued)

larotrectinib

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

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Colon Cancer [Version 2.2021]

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larotrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Cutaneous; Metastatic, Unresectable, Progression (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Cutaneous Melanoma [Version 2.2021]

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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):
- Adenocarcinoma, Squamous Cell; Unresectable, Locally Advanced, Recurrent, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Esophageal and Esophagogastric Junction Cancers [Version 1.2021]

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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, Metastatic (Second-line therapy, Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Gastric Cancer [Version 2.2021]

TPM3-NTRK1 fusion (continued)

larotrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unresectable, Progression (Subsequent therapy); Useful in certain circumstances

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

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larotrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Salivary Gland Neoplasm; Recurrent, Unresectable, Distant Metastases (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Head and Neck Cancers [Version 2.2021]

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larotrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Gallbladder Cancer, Intrahepatic, Extrahepatic; Unresectable, Metastatic (First-line therapy); Useful in certain circumstances
- Gallbladder Cancer, Intrahepatic, Extrahepatic; Progression (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 1.2021]

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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 1.2021]

TPM3-NTRK1 fusion (continued)

larotrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Epithelial, Less Common Ovarian Cancers, Fallopian Tube, Primary Peritoneal; Recurrent (Recurrence therapy); Useful in certain circumstances

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

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larotrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Adenocarcinoma; Metastatic (First-line therapy); Useful in certain circumstances
- Adenocarcinoma; Locally Advanced, Metastatic, Recurrent (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2021]

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larotrectinib

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

NCCN Recommendation category: 2A

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

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

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larotrectinib

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

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Unspecified histology; Advanced, Metastatic (First-line therapy); Useful in certain circumstances

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

TPM3-NTRK1 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):
- Locally Recurrent, Advanced, Metastatic (Line of therapy not specified)

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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larotrectinib

Cancer type: Thyroid Gland Anaplastic Carcinoma

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- Stage IVC; Metastatic (Line of therapy not specified); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 3.2020]

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entrectinib

Cancer type: Cervical Cancer

Variant class: NTRK fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Recurrent, Metastatic (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):
- Adenocarcinoma; Metastatic (First-line therapy); Useful in certain circumstances
- Adenocarcinoma; Locally Advanced, Metastatic, Recurrent (Subsequent therapy); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Pancreatic Adenocarcinoma [Version 2.2021]

TPM3-NTRK1 fusion (continued)

entrectinib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Advanced, Recurrent (Line of therapy not specified); Useful in certain circumstances

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

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entrectinib

Cancer type: Uterine Sarcoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Recurrent, Metastatic, Progression (Line of therapy not specified); Useful in certain circumstances

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

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larotrectinib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Recurrent, Metastatic (Second-line therapy); Useful in certain circumstances

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

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larotrectinib

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

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Advanced, Recurrent (Line of therapy not specified); Useful in certain circumstances

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

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larotrectinib

Cancer type: Uterine Sarcoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2B

Population segment (Line of therapy):
- Recurrent, Metastatic, Progression (Line of therapy not specified); Useful in certain circumstances

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

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 2021-04-14. For the most up-to-date information, search www.ema.europa.eu/ema.

TPM3-NTRK1 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

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 2021-04-01. For the most up-to-date information, search www.esmo.org.

TPM3-NTRK1 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 (Line of therapy 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

TPM3-NTRK1 fusion

NCT ID	Title	Phase
NCT03574402	An Open-label, Multi-center, Phase II Umbrella Study to Assess Efficacy of Targeted Therapy or Immunotherapy Directed by Next Generation Sequencing (NGS) in Chinese Patients With Advanced NSCLC (TRUMP)	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
NCT04302025	NAUTIKA1: Multicenter, Phase II, Neoadjuvant and Adjuvant Study of Alectinib, Entrectinib, Vemurafenib Plus Cobimetinib, or Pralsetinib in Patients With Resectable Stages II-III Non-Small Cell Lung Cancer With ALK, ROS1, NTRK, BRAF V600, or RET Molecular Alterations	II
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy	II
NCT02576431	A Phase II Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects With NTRK Fusion-positive Tumors	II
NCT01639508	A Phase II Study of Cabozantinib in Patients With RET Fusion-Positive Advanced Non-Small Cell Lung Cancer and Those With Other Genotypes: ROS1 or NTRK Fusions or Increased MET or AXL Activity	II
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II
No NCT ID	Single arm, Open Label, Signal Seeking, Phase IIa Trial of the Activity of Larotrectinib in Patients with Advanced NTRK1-3 Positive Tumours.	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

Clinical Trials Summary (continued)

TPM3-NTRK1 fusion (continued)

NCT ID	Title	Phase
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
NCT03215511	A Phase I/II Study of the TRK Inhibitor Selitrectinib in Adult and Pediatric Subjects With Previously Treated NTRK Fusion Cancers	I/II
NCT03556228	An Open-Label, Multiple-Dose, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics, and Pharmacodynamics of VMD-928 in Subjects With Solid Tumors or Lymphoma	I
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
NCT04685226	A Multicenter, Nonrandomized, Open-Label Phase I/II Clinical Trial to Evaluate the Safety, Tolerability, and Pharmacokinetics of ICP-723 in Patients With Solid Tumors	I/II
NCT04671849	An Open Label, Multi-center, Phase I Clinical Study to Evaluate the Safety, Effectiveness and Pharmacokinetic Characteristics of SIM1803-1A in Patients With Locally Advanced/Metastatic Solid Tumors With NTRK, ROS1 or ALK Gene Fusion Mutations.	I

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-04-14. For the most up-to-date information, search www.fda.gov.

TPM3-NTRK1 fusion

repotrectinib

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

Supporting Statement:

The FDA has granted Breakthrough Therapy Designation to repotrectinib for:

- ROS1-positive metastatic non-small cell lung cancer (NSCLC) that has not been treated with a ROS1 tyrosine kinase inhibitor (TKI).

The FDA has granted Fast Track Designation to repotrectinib for:

- ROS1-positive non-small cell lung cancer (NSCLC) previously treated with one prior platinum chemotherapy and one prior ROS1 TKI.
- NTRK-positive advanced solid tumors that have progressed following treatment with at least one prior line of chemotherapy and one or two prior TRK TKIs.

Reference:

https://www.globenewswire.com/news-release/2020/12/08/2141343/0/en/Turning-Point-Therapeutics-Granted-FDA-Breakthrough-Therapy-Designation-for-Repotrectinib-Treatment-in-Patients-with-ROS1-Positive-Metastatic-Non-Small-Cell-Lung-Cancer-Who-Have-No.html

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-04-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

TPM3-NTRK1 fusion

larotrectinib

Cancer type: Angiosarcoma, Pleomorphic Rhabdomyosarcoma

Variant class: NTRK fusion

Summary:

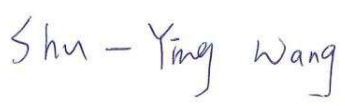
NCCN Guidelines® include the following supporting statement(s):

- "Not recommended for angiosarcoma or pleomorphic rhabdomyosarcoma."

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

Signatures

Testing Personnel:



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Laboratory Supervisor:

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Pathologist:

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References

1. Bibel et al. Neurotrophins: key regulators of cell fate and cell shape in the vertebrate nervous system. Genes Dev. 2000 Dec 1;14(23):2919-37. PMID: 11114882
2. Martin-Zanca et al. A human oncogene formed by the fusion of truncated tropomyosin and protein tyrosine kinase sequences. Nature. 1986 Feb 27-Mar 5;319(6056):743-8. PMID: 2869410
3. Amatu et al. NTRK gene fusions as novel targets of cancer therapy across multiple tumour types. ESMO Open. 2016 Mar 18;1(2):e000023. eCollection 2016. PMID: 27843590
4. Lange et al. Inhibiting TRK Proteins in Clinical Cancer Therapy. Cancers (Basel). 2018 Apr 4;10(4). PMID: 29617282
5. Vaishnavi et al. TRKing down an old oncogene in a new era of targeted therapy. Cancer Discov. 2015 Jan;5(1):25-34. PMID: 25527197
6. Weinstein et al. The Cancer Genome Atlas Pan-Cancer analysis project. Nat. Genet. 2013 Oct;45(10):1113-20. PMID: 24071849
7. Kim et al. NTRK1 fusion in glioblastoma multiforme. PLoS ONE. 2014;9(3):e91940. PMID: 24647444
8. Gatalica et al. Molecular characterization of cancers with NTRK gene fusions. Mod. Pathol. 2019 Jan;32(1):147-153. PMID: 30171197
9. Vaishnavi et al. Oncogenic and drug-sensitive NTRK1 rearrangements in lung cancer. Nat. Med. 2013 Nov;19(11):1469-1472. PMID: 24162815
10. Rubin et al. Congenital mesoblastic nephroma t(12;15) is associated with ETV6-NTRK3 gene fusion: cytogenetic and molecular relationship to congenital (infantile) fibrosarcoma. Am. J. Pathol. 1998 Nov;153(5):1451-8. PMID: 9811336
11. Brzeziańska et al. Molecular analysis of the RET and NTRK1 gene rearrangements in papillary thyroid carcinoma in the Polish population. Mutat. Res. 2006 Jul 25;599(1-2):26-35. PMID: 16483615
12. Wu et al. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat. Genet. 2014 May;46(5):444-450. PMID: 24705251
13. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210861s006lbl.pdf
14. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212726s000lbl.pdf
15. Fuse et al. Mechanisms of Resistance to NTRK Inhibitors and Therapeutic Strategies in NTRK1-Rearranged Cancers. Mol. Cancer Ther. 2017 Oct;16(10):2130-2143. PMID: 28751539
16. https://www.globenewswire.com/news-release/2020/12/08/2141343/0/en/Turning-Point-Therapeutics-Granted-FDA-Breakthrough-Therapy-Designation-for-Repotrectinib-Treatment-in-Patients-with-ROS1-Positive-Metastatic-Non-Small-Cell-Lung-Cancer-Who-Have-No.html