Taipei Veterans General Hospital

Department of Pathology and Laboratory Medicine
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Sample Information

Patient Name: 唐志珊
Gender: Female
ID No.: C201017291
History No.: 31850836
Age: 70

Ordering Doctor: DOC2095G 蔡宜芳
Ordering REQ.: D6ED6E1
Signing in Date: 2021/09/02

Path No.: S110-99442
MP No.: F21071
Assay: Oncomine Focus Assay
Sample Type: FFPE
Block No.: S110-24704M
Percentage of tumor cells: 75%

Reporting Doctor: DOC5466K 葉奕成 (Phone: 8#5466)

Note:

Sample Cancer Type: Breast Cancer

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Relevant Breast Cancer Variants

Gene	Finding
ERBB2	None detected
PIK3CA	***PIK3CA p.(E542K) c.1624G>A***

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 transcription factor 6 - neurotrophic receptor tyrosine kinase 3	**entrectinib** [1, 2] **larotrectinib** [1]	entrectinib larotrectinib	4

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.

Relevant Biomarkers (continued)

Tier	Genomic Alteration	Relevant Therapies (In this cancer type)	Relevant Therapies (In other cancer type)	Clinical Trials
		TRK inhibitor		
IA	*PIK3CA p.(E542K) c.1624G>A* phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha Allele Frequency: 8.94%	**alpelisib + hormone therapy** [1, 2]	None	3

Public data sources included in relevant therapies: FDA[1], 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.

Variant Details

DNA Sequence Variants

Gene	Amino Acid Change	Coding	Variant ID	Locus	Allele Frequency	Transcript	Variant Effect	Coverage
PIK3CA	p.(E542K)	c.1624G>A	COSM760	chr3:178936082	8.94%	NM_006218.4	missense	1701
ALK	p.(*1621R)	c.4861T>C	.	chr2:29416092	4.35%	NM_004304.5	stoploss	2000
FGFR4	p.(P136L)	c.407C>T	.	chr5:176517797	99.85%	NM_213647.3	missense	2000
EGFR	p.(Q787=)	c.2361G>A	.	chr7:55249063	48.60%	NM_005228.5	synonymous	2000
RET	p.(S904=)	c.2712C>G	.	chr10:43615633	48.15%	NM_020975.6	synonymous	1996
MAP2K2	p.(V64=)	c.192C>T	.	chr19:4117528	49.10%	NM_030662.4	synonymous	2000

Gene Fusions (RNA)

Genes	Variant ID	Locus	Read Count
ETV6-NTRK3	ETV6-NTRK3.E4N15.COSF823.1	chr12:12006495 - chr15:88483984	217
ETV6-NTRK3	ETV6-NTRK3.E5N15.COSF571.1	chr12:12022903 - chr15:88483984	147205

Biomarker Descriptions

ETV6 (ETS variant transcription factor 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,

Biomarker Descriptions (continued)

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 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.

PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha)

Background: The PIK3CA gene encodes the phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha of the class I phosphatidylinositol 3-kinase (PI3K) enzyme[34]. PI3K is a heterodimer that contains a p85 regulatory subunit, which couples one of four p110 catalytic subunits to activated tyrosine protein kinases[35,36]. The p110 catalytic subunits include p110α, β, δ, γ and are encoded by genes PIK3CA, PIK3CB, PIK3CD, and PIK3CG, respectively[35]. PI3K catalyzes the conversion of phosphatidylinositol (4,5)-bisphosphate (PI(4,5)P2) into phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)P3) while the phosphatase and tensin homolog (PTEN) catalyzes the reverse reaction[37,38]. The reversible phosphorylation of inositol lipids regulates diverse aspects of cell growth and metabolism[37,38,39,40]. Recurrent somatic alterations in PIK3CA are frequent in cancer and result in the activation of PI3K/AKT/MTOR pathway, which can influence several hallmarks of cancer including cell proliferation, apoptosis, cancer cell metabolism and invasion, and genetic instability[41,42,43].

Alterations and prevalence: Recurrent somatic activating mutations in PIK3CA are common in diverse cancers and are observed in 20-30% of breast, cervical, and uterine cancers and 10-20% of bladder, gastric, head and neck, and colorectal cancers[13,44]. Activating mutations in PIK3CA commonly cluster in two regions corresponding to the exon 9 helical (codons E542/E545) and exon 20 kinase (codon H1047) domains, each having distinct mechanisms of activation[45,46,47]. PIK3CA resides in the 3q26 cytoband, a region frequently amplified (10-30%) in diverse cancers including squamous carcinomas of the lung, cervix, head and neck, and esophagus, and in serous ovarian and uterine cancers[13,44].

Potential relevance: The PI3K inhibitor, alpelisib[48], is FDA approved (2019) in combination with fulvestrant for the treatment of patients with PIK3CA-mutated, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced or metastatic breast cancer. Additionally, a phase Ib study of alpelisib with letrozole in patients with metastatic estrogen receptor (ER)-positive breast cancer, the clinical benefit rate, defined as lack of disease progression ≥ 6 months, was 44% (7/16) in PIK3CA-mutated tumors and 20% (2/20) in PIK3CA wild-type tumors[49]. Specifically, exon 20 H1047R mutations were associated with more durable

Biomarker Descriptions (continued)

clinical responses in comparison to exon 9 E545K mutations[49]. However, alpelisib did not improve response when administered with letrozole in patients with ER+ early breast cancer with PIK3CA mutations[50]. Case studies with MTOR inhibitors sirolimus and temsirolimus report isolated cases of clinical response in PIK3CA mutated refractory cancers[51,52].

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	✖	✖	✖	●	✖
repotrectinib	✖	✖	✖	✖	● (I/II)

PIK3CA p.(E542K) c.1624G>A

Relevant Therapy	FDA	NCCN	EMA	ESMO	Clinical Trials*
alpelisib + fulvestrant	●	●	●	●	✖
inavolisib, palbociclib, hormone therapy	✖	✖	✖	✖	● (II/III)
inavolisib	✖	✖	✖	✖	● (II)
hormone therapy, alpelisib	✖	✖	✖	✖	● (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 2021-07-14. 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/2019/212725s000lbl.pdf

● 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

PIK3CA p.(E542K) c.1624G>A

alpelisib + fulvestrant

Cancer type: Breast Cancer **Label as of:** 2020-09-01 **Variant class:** PIK3CA E542K mutation

Other criteria: ERBB2 negative, Hormone receptor positive

Indications and usage:
PIQRAY® is a kinase inhibitor indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with hormone receptor (HR)- positive, human epidermal growth factor receptor 2 (HER2)-negative, PIK3CA-mutated, advanced or metastatic breast cancer as detected by an FDA-approved test following progression on or after an endocrine-based regimen.

Reference:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212526s001lbl.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 2021-07-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

ETV6-NTRK3 fusion

● 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 5.2021]

● 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 1.2021]

● 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 5.2021]

● 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 1.2021]

ETV6-NTRK3 fusion (continued)

entrectinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** NTRK3 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 5.2021]

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larotrectinib

Cancer type: Non-Small Cell Lung Cancer **Variant class:** NTRK3 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 5.2021]

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entrectinib

Cancer type: Anaplastic Astrocytoma, Anaplastic Oligoastrocytoma, Anaplastic Oligodendroglioma, Glioblastoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2021]

ETV6-NTRK3 fusion (continued)

entrectinib

Cancer type: Ganglioglioma, Pilocytic Astrocytoma, Pleomorphic Xanthoastrocytoma, Subependymal Giant Cell Astrocytoma

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade I, WHO CNS Tumor Grade II; Recurrent, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2021]

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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: Cutaneous Melanoma

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- 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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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 3.2021]

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

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

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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]

---

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 3.2021]

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entrectinib

Cancer type: Hepatocellular Carcinoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 3.2021]

ETV6-NTRK3 fusion (continued)

entrectinib

Cancer type: Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma

Variant class: NTRK fusion

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 3.2021]

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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]

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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-Rectal Cancer [Version 1.2021]

ETV6-NTRK3 fusion (continued)

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 2.2021]

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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 1.2021]

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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 IVA, Stage IVB; Local, Unresectable (Neoadjuvant therapy)
- Stage IVC; Metastatic (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 1.2021]

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larotrectinib

Cancer type: Anaplastic Astrocytoma, Anaplastic Oligoastrocytoma, Anaplastic Oligodendroglioma, Glioblastoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [Version 1.2021]

ETV6-NTRK3 fusion (continued)

larotrectinib

Cancer type: Ganglioglioma, Pilocytic Astrocytoma, Pleomorphic Xanthoastrocytoma, Subependymal Giant Cell Astrocytoma

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- WHO CNS Tumor Grade I, WHO CNS Tumor Grade II; Recurrent, Progression (Line of therapy not specified); Useful in certain circumstances

Reference: NCCN Guidelines® - NCCN-Central Nervous System Cancers [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 (Subsequent therapy)

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

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larotrectinib

Cancer type: Cutaneous Melanoma

Variant class: NTRK fusion

NCCN Recommendation category: 2A

Population segment (Line of therapy):
- 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 3.2021]

ETV6-NTRK3 fusion (continued)

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 3.2021]

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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 3.2021]

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larotrectinib

Cancer type: Hepatocellular Carcinoma **Variant class:** NTRK fusion

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 3.2021]

ETV6-NTRK3 fusion (continued)

larotrectinib

Cancer type: Extrahepatic Cholangiocarcinoma, Gallbladder Carcinoma, Intrahepatic Cholangiocarcinoma

Variant class: NTRK fusion

NCCN Recommendation category: 2A

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

Reference: NCCN Guidelines® - NCCN-Hepatobiliary Cancers [Version 3.2021]

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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]

ETV6-NTRK3 fusion (continued)

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 2.2021]

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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 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):
- Stage IVA, Stage IVB; Local, Unresectable (Neoadjuvant therapy)
- Stage IVC; Metastatic (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Thyroid Carcinoma [Version 1.2021]

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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]

ETV6-NTRK3 fusion (continued)

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]

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entrectinib

Cancer type: Endometrial Carcinoma **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 3.2021]

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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 3.2021]

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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 Carcinoma **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 3.2021]

ETV6-NTRK3 fusion (continued)

○ 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 3.2021]

PIK3CA p.(E542K) c.1624G>A

● alpelisib + fulvestrant

Cancer type: Breast Cancer **Variant class:** PIK3CA activating mutation

Other criteria: ERBB2 negative, Hormone receptor positive

NCCN Recommendation category: 1

Population segment (Line of therapy):
- Stage IV; Recurrent, Invasive, Unresectable, Local (Second-line therapy); Preferred intervention

Reference: NCCN Guidelines® - NCCN-Breast Cancer [Version 5.2021]

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 2021-07-14. 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

PIK3CA p.(E542K) c.1624G>A

● alpelisib + fulvestrant

Cancer type: Breast Cancer **Label as of:** 2021-05-26 **Variant class:** PIK3CA E542K mutation

Other criteria: ERBB2 negative, Hormone receptor positive

Reference:

https://www.ema.europa.eu/en/documents/product-information/piqray-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 2021-07-01. 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 (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)]

PIK3CA p.(E542K) c.1624G>A

● alpelisib + fulvestrant

Cancer type: Breast Cancer **Variant class:** PIK3CA exon 9 mutation

Other criteria: ERBB2 negative, ER positive

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

Population segment (Line of therapy):
- Luminal A, Luminal B; Advanced (Line of therapy not specified); ESMO-MCBS v1.1 score: 3

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 in Taiwan region:

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
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	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

PIK3CA p.(E542K) c.1624G>A

NCT ID	Title	Phase
NCT04191499	A Phase III, Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of GDC-0077 Plus Palbociclib and Fulvestrant Versus Placebo Plus Palbociclib and Fulvestrant in Patients With PIK3CA-Mutant, Hormone Receptor-Positive, Her2-Negative, Locally Advanced or Metastatic Breast Cancer	II/III
NCT04188548	EMBER: A Phase Ia/Ib Study of LY3484356 Administered as Monotherapy and in Combination With Anticancer Therapies for Patients With ER+ Locally Advanced or Metastatic Breast Cancer and Other Select Non-Breast Cancers	I
NCT04589845	Tumor-Agnostic Precision Immunooncology and Somatic Targeting Rational for You (TAPISTRY) Phase II Platform Trial	II

Alerts Informed By Public Data Sources

Current FDA Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

FDA information is current as of 2021-07-14. For the most up-to-date information, search www.fda.gov.

ETV6-NTRK3 fusion

repotrectinib

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

Supporting Statement:

The FDA has granted Fast Track Designation to the ALK/ROS1/TRK inhibitor, repotrectinib, for:

- ROS1-positive advanced non-small cell lung cancer (NSCLC) previously treated with one prior platinum chemotherapy and one prior ROS1 TKI.
- ROS1-positive advanced non-small cell lung cancer (NSCLC) without prior ROS1 TKI treatment.
- NTRK fusion 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://ir.tptherapeutics.com/news-releases/news-release-details/turning-point-therapeutics-granted-fast-track-designation

Current NCCN Information

Contraindicated Not recommended Resistance Breakthrough Fast Track

NCCN information is current as of 2021-07-01. For the most up-to-date information, search www.nccn.org.
For NCCN International Adaptations & Translations, search www.nccn.org/global/international_adaptations.aspx.

ETV6-NTRK3 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 2.2021]

Signatures

Testing Personnel:

2021.09.03
10:26:44 +08'00'

Laboratory Supervisor:

2021.09.03
10:27:01 +08'00'

Pathologist:

2021.09.03
10:27:22 +08'00'

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