ECOG-ACRIN
cancer research group
Reshaping the future of patient care

November 10, 2022

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #31 to EAY131-Z1E, *Molecular Analysis for Therapy Choice (MATCH): MATCH Treatment Subprotocol Z1E: LOXO-101 in Patients with Tumors with NTRK Fusions.*

This addendum is in response to Dr. John Wright, Dr. Jeffrey Moscow, and Dr. Meg Mooney September 22, 2022 Request for Rapid Amendment for LOXO-101.

The following revisions to EAY131-Z1E protocol have been made in this addendum:

	Section	**Change**
1.	Cover Page	Updated Version Date.
2.	3.3	Updated the LOXO-101 CAEPR list with version 2.3, May 12, 2022.

The following revisions to EAY131-Z1E Informed Consent Document have been made in this addendum:

	Section	**Change**
1.	Cover Page	Updated Version Date.
2.	What possible risks can I expect from taking part in this study?	Updated the possible risks language and the LOXO-101 risk list with version 2.3, May 12, 2022.

If you have any questions regarding this addendum, please contact eradomyshelsky@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to EAY131-Z1E so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director of Protocol Development

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ECOG-ACRIN cancer research group
Reshaping the future of patient care

EAY131-Z1E

Molecular Analysis for Therapy Choice (MATCH)

MATCH Treatment Subprotocol Z1E: Larotrectinib (LOXO-101) in Patients with Tumors with NTRK Fusions

LAROTRECTINIB (LOXO-101) TREATMENT SUBPROTOCOL CHAIR: David S. Hong, MD

Rev. Add29

Version Date: November 10, 2022

NOTE: This subprotocol (EAY131-Z1E) should be used in conjunction with the MATCH Master Protocol (EAY131).

NOTE: As of 11/17, all protocol changes will be noted by addendum number.

SUBPROTOCOL ACTIVATION DATE

March 13, 2017 (Incorporated in Addendum #7)
Addendum #12
Addendum #13
Addendum #14
Addendum #17
Addendum #23
Addendum #25
Addendum #29
Addendum #31

Agent	IND#	NSC#	Supply
Larotrectinib (LOXO-101)	IND Sponsor: DCTD, NCI IND#: [redacted]	788607	NCI Supplied

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TREATMENT SUBPROTOCOL CHAIR

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Schema

Cycle = 28 days
Accrual Goal: 35

1. Introduction

1.1 LOXO-101

1.1.1 *NTRK* Gene Family and TRK Proteins

The human NTRK genes encode a family of TRK (tropomyosin-related kinase) receptor tyrosine kinases, neurotrophin receptors that are expressed in a variety of tissue types. *NTRK1, NTRK2* and *NTRK3* encode TRKA, TRKB and TRKC, respectively. The in vivo ligands for TRKA are neurotrophic growth factor (NGF) and neurotrophin-3 (NT-3); the ligands for TRKB are brain-derived neurotrophic factor (BDNF) and NT-4; and the ligand for TRKC is NT-3. The TRK receptor family is involved in neuronal development, including the growth and function of neuronal synapses, memory and development, neuronal maintenance, and the protection of neurons after ischemia or other injuries [1].

TRK proteins function normally through ligand-mediated dimerization, leading to catalytic activation via cross-phosphorylation of tyrosine moieties within the cytoplasmic-facing region of the dimerization partner. This activation leads to downstream signaling through multiple pathways, including the PI3 kinase pathway, phospholipase C-gamma, the Erk1 and Erk2 mitogen-activated protein (MAP) kinase pathway, and the Erk5 MAP kinase pathway. The propagation of these signals can stimulate growth, survival and differentiation [2].

Oncogenic activity of TRK proteins has been described in a variety of malignancies. Following the paradigm of other established oncogenic drivers, TRK proteins are thought to acquire oncogenic activity via *NTRK* gene rearrangements, leading to mis-expression of fusion proteins with a capacity for ligand-independent dimerization and downstream pathway activation. The typical gene structure of such an oncogenic fusion involves the 3’ region of a proto-oncogene (encoding the kinase domain) juxtaposed to 5’ sequences from an unrelated gene via intra- or inter-chromosomal rearrangement. The resultant novel oncogene is both aberrantly expressed and has constitutive activation of the kinase domain.

Oncogenic TRK fusions were first identified in a colorectal cell line [3]]. Since then, *NTRK* gene rearrangements and their corresponding TRK fusions have been described in a variety of solid tumor malignancies, including thyroid cancer, glioblastoma multiforme, non-small cell lung cancer, colon adenocarcinoma, head and neck squamous cell carcinoma, and soft tissue sarcoma. A summary of TRK fusions in cancer is shown in Table 1.

Table 1: Estimated Frequencies of NTRK Gene Fusions in Malignancies

NTRK Gene Fusion	Cancer Type	Estimated Frequency			
		<4%	2-25%	>25%	Ref.
NTRK1	Spitz neoplasms nevi		X		[4]
NTRK1	Glioblastoma	X			[5]
NTRK1	Intrahepatic cholangiocarcinoma	X			[6]
NTRK1	Sarcoma	X			[7]
NTRK2	Astrocytoma	X			[8]
NTRK3	Mammary analogue secretory carcinoma (MASC) of the salivary glands			X	[9]
NTRK3	Secretory breast carcinoma			X	[10]
NTRK3	Congenital mesoblastic nephroma		X		[11, 12]
NTRK3	Acute myeloid leukemia	X			[13]
NTRK3	Breast invasive carcinoma	X			[7]
NTRK3	Skin cutaneous melanoma	X			[7]
NTRK1/2	Lung adenocarcinoma	X			[7][14][15]
NTRK1/3	Papillary thyroid		X		[16-18]
NTRK1/3	Colorectal cancer	X			[7][19]
NTRK2/3	Brain low-grade glioma	X			[7]
NTRK2/3	Head and neck squamous cell carcinoma	X			[7]
NTRK1/2/3	Pontine glioma		X		[20]

The dependence of some tumors on oncogenic signaling via receptor tyrosine kinase fusions has been well established in several contexts. Cancers with chromosomal rearrangements that result in fusion kinases demonstrate oncogene-dependent behavior and dramatic sensitivity to inhibition of kinase signaling by targeted therapies [21-23]. Tumors with fusion kinases involving Abelson murine leukemia viral oncogene homolog (ABL), anaplastic lymphoma kinase (ALK), and human analog of the v-ros retroviral gene (ROS1) may be treated with currently Food and Drug Administration (FDA)-approved drugs, while other tumors with fusions in RET, FGFR2 and FGFR3 have shown promising sensitivity to experimental agents in phase 1 and phase 2 studies [24].

1.1.2 Larotrectinib (LOXO-101) Chemistry and Description

Larotrectinib (LOXO-101) is an orally bioavailable, adenosine triphosphate (ATP)-competitive, selective small molecule inhibitor of TRKA, TRKB and TRKC. Larotrectinib (LOXO-101) is a small molecule with an empirical formula of C21H24F2N6O6S [IB Figure 3-

1] and a molecular weight of 526.52 (428.4 as the free base). The chemical name is (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate.

In biochemical assays, Larotrectinib (LOXO-101) binds TRKA, TRKB, and TRKC and inhibits signaling with IC50 values in the low nanomolar range. In cell lines engineered to express TRK fusion proteins, Larotrectinib (LOXO-101) inhibits cell viability in vitro and causes stabilization or regression of xenograft tumors [25] [IB Table 4-1, Figure 4-1, Figure 4-2]. Larotrectinib (LOXO-101) is highly specific for TRK protein inhibition, with > 1000-fold greater selective inhibition of TRK proteins over other kinases. Consistent with this high degree of selectivity, Larotrectinib (LOXO-101) has no anti-proliferative effect in tumor cell lines that do not active TRK proteins.

Additional information may be found in the Investigator's Brochure.

1.2 Larotrectinib (LOXO-101) Clinical Experience

1.2.1 LOXO-101 Clinical Experience

The first-in-human clinical study (Study LOXO-TRK-14001) was initiated in May 2014 and is multicenter, open-label, Phase 1, dose-escalation study in adult patients with advanced solid tumors. The initial cohort was 50 mg orally, once daily for 28-day cycles, with dose escalations planned to increase to 300 mg twice daily. As of March 26, 2015, 15 patients had enrolled and the plasma concentrations for Larotrectinib (LOXO-101) that showed Larotrectinib (LOXO-101) had apparent oral clearance (CL/F) of approximately 0.6 L/h/kg and a plasma half-life of 2-3 hours. Exposure was similar on Day 1 and at steady-state; there was no accumulation of Larotrectinib (LOXO-101). Low concentrations of Larotrectinib (LOXO-101) were recovered as unchanged drug in urine indicating that renal clearance is a minor contributor to the overall clearance of Larotrectinib (LOXO-101). Larotrectinib (LOXO-101) is a substrate for brain efflux transporters Pglycoprotein (P-gp) and breast cancer resistance protein (BCRP) and has low distribution into the brain; brain levels in rats are estimated to be approximately 2-5% those in plasma, but nevertheless potentially sufficient for partial inhibition of TRK receptors in the brain at the doses studied thus far in humans.

Larotrectinib (LOXO-101) has been evaluated at 100 mg BID, which was deemed safe by the Protocol Safety Review Committee. Larotrectinib (LOXO-101) has been well-tolerated at all dose levels tested, with the most common adverse events, regardless of attribution, being Grade 1 and 2 fatigue, dizziness and anemia (Burris, 2015). All adverse events seen in more than 2 patients, or grade 3 or 4 adverse events seen in more than 1 patient are listed in Table 2.

Table 2: Treatment-emergent Adverse Events in Study LOXO-TRK-14001		
Adverse Events	All Grade	Grades 3-4
	Number (%)	Number (%)
Fatigue	7 (47)	1 (7)
Dizziness	4 (27)	0
Anemia	5 (33)	2 (13)
Constipation	3 (20)	0
Dry mouth	3 (20)	0
Diarrhea	2 (13)	0
Nausea	2 (13)	0
Vomiting	2 (13)	0
Chills	2 (13)	0
Pyrexia	2 (13)	0
ALP increased	2 (13)	0
Hyperglycemia	2 (13)	0
Hypokalemia	2 (13)	0
Peripheral edema	2 (13)	0
Syncope	2 (13)	2 (13)
Cough	2 (13)	0
Rash	2 (13)	0
AST increased	1 (7)	1 (7)
Delirium	1 (7)	1 (7)
Pneumonia	1 (7)	1 (7)

As of March 25, 2016, seven patients with *NTRK* gene fusions had been enrolled on the Phase 1 study, and six of these had undergone response assessment. Five of these six demonstrated confirmed partial response by RECIST 1.1 criteria. The sixth patient demonstrated stable disease with 18% reduction in tumor size by RECIST 1.1. Responses have been durable, with the longest response being 14 cycles and ongoing. None of the patients on the phase 1 study with NTRK gene fusions have discontinued study drug. Responses have not been observed in patients lacking an *NTRK* gene fusion.

2. Selection of Patients

Each of the criteria in the checklist that follows must be met, along with the eligibility in the MATCH Master Protocol, in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 2 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 2 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.Execofficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

NOTE: All patients must have signed the relevant treatment consent form

2.1 Eligibility Criteria

_____ 2.1.1 Patients must fulfill all eligibility criteria outlined in Section 3.1 of MATCH Master Protocol (excluding Section 3.1.6) at the time of registration to treatment step (Step 1, 3, 5, 7).

Rev. Add13

_____ 2.1.2 Patients must have a malignancy harboring an NTRK1, NTRK2 or NTRK3 gene fusion, as determined by the MATCH screening assessment and described in Appendix II. See Appendix II for information on the NTRK fusions and corresponding Levels of Evidence.

_____ 2.1.3 Patients must have an electrocardiogram (ECG) within 8 weeks prior to treatment assignment and must have no clinically important abnormalities in rhythm, conduction or morphology of resting ECG (e.g. complete left bundle branch block, third degree heart block).

Date of ECG: _____

_____ 2.1.4 Patients must not have known hypersensitivity to Larotrectinib (LOXO-101) or compounds of similar chemical or biologic composition.

_____ 2.1.5 Patients with inability to discontinue treatment with a strong CYP3A4 inhibitor or inducer prior to start of treatment are excluded.

_____ 2.1.6 Patients who have previously received treatment with a TRKA, TRKB, or TRKC inhibitor are excluded. Such inhibitors include Larotrectinib (LOXO-101) , entrectinib (RXDX-101), TSR-011, DS6051, Altiratinib (DCC-2701), MGCD516, Dovitinib (TKI258, CHIR528), AZD7451, PLX7486, and BIBF1120.

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

3. Larotrectinib (LOXO-101) Treatment Plan

3.1 Administration Schedule

All study subjects will receive LOXO-101 at a starting dose of 100 mg orally BID, with administration at consistent times each day and doses separated by approximately 12 hours. Doses may be taken without regard to food. A cycle is 28-days.

If a subject vomits after taking study medication, the subject should be instructed not to retake the dose and should take the next scheduled dose.

If a dose of Larotrectinib (LOXO-101) is missed, only take the dose if it is more than 8 hours until the next scheduled dose.

3.2 Adverse Event Reporting Requirements

The Adverse Event Reporting Requirements for all EAY131 subprotocols are outlined in the MATCH MASTER protocol. Please refer to those guidelines when determining if an event qualifies as a Serious Adverse Event (SAE) and requires expedited reporting via CTEP's Adverse Event Reporting System (CTEP-AERS).

In addition, the following section outlines agent specific requirements and must be followed to ensure all reporting requirements are met.

3.2.1 Additional instructions, requirements and exceptions for protocol EAY131 – Subprotocol Z1E

Additional Instructions

For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

EAY131 – Subprotocol Z1E specific expedited reporting requirements:

Rev. Add25

- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on Larotrectinib (LOXO-101) , or within 28 days of the female patient's last dose of lLarotrectinib (LOXO-101) , are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge. Please refer to Appendix VIII in MATCH Master Protocol for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EAY131 – Subprotocol Z1E specific expedited reporting exceptions:

For Subprotocol Z1E, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

Rev. Add29

3.2.2 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported as follows:

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days
  2. Report the diagnosis on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy

     NOTE: When reporting attribution on the AE Form, assess the relationship between the secondary malignancy and the current protocol treatment ONLY (and NOT relationship to any anti-cancer treatment received either before or after protocol treatment).
  3. Report the diagnosis via CTEP-AERS at http://ctep.cancer.gov
  4. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.

5. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. Add12
Rev. Add17
Rev. Add23
Rev. Add31

3.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Larotrectinib (LOXO-101) (NSC 788607)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 388 patients.* Below is the CAEPR for Larotrectinib (LOXO-101).

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event in the SPEER

Version 2.3, May 12, 2022[1]

Adverse Events with Possible Relationship to Larotrectinib sulfate (BAY 2757556, LOXO-101) (CTCAE 5.0 Term) [n= 388]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
	Diarrhea		***Diarrhea (Gr 2)***
	Nausea		***Nausea (Gr 2)***
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
	Fatigue		***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
		Gait disturbance	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Weight gain		***Weight gain (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Myalgia		***Myalgia (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
		Paresthesia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on Larotrectinib sulfate (BAY 2757556, LOXO-101) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Larotrectinib sulfate (BAY 2757556, LOXO-101) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block first degree; Cardiac disorders - Other (left ventricular dysfunction); Pericardial effusion

ENDOCRINE DISORDERS - Hypothyroidism

EYE DISORDERS - Eye pain; Periorbital edema; Watering eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dry mouth; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (enterocutaneous fistula); Gastrointestinal disorders - Other (gastrointestinal obstruction); Gastrointestinal disorders - Other (teething); Oral pain; Small intestinal obstruction; Small intestinal perforation

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Facial pain; Flu like symptoms; Multi-organ failure; Pain

HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (bile duct obstruction); Hepatobiliary disorders - Other (hepatic function abnormal); Hepatobiliary disorders - Other (jaundice cholestatic)

IMMUNE SYSTEM DISORDERS - Allergic reaction

INFECTIONS AND INFESTATIONS - Hepatitis viral; Laryngitis; Lung infection; Sepsis; Skin infection; Upper respiratory infection; Urinary tract infection; Vaginal infection; Viremia; Wound infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall

INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; Ejection fraction decreased; Electrocardiogram QT corrected interval prolonged; Investigations - Other (hepatic cytolysis); Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Anorexia; Dehydration; Hypercalcemia; Hyperglycemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Flank pain; Generalized muscle weakness; Joint range of motion decreased; Musculoskeletal and connective tissue disorder - Other (muscle twitching); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (acute myeloid leukemia); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (bile duct adenocarcinoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (glioma, glioblastoma multiforme); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (malignant neoplasm progression, neoplasm progression); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastases to central nervous system)

NERVOUS SYSTEM DISORDERS - Ataxia; Depressed level of consciousness; Dysarthria; Dysesthesia; Dysgeusia; Edema cerebral; Extrapyramidal disorder; Headache; Memory impairment; Nervous system disorders - Other (motor dysfunction); Peripheral sensory neuropathy; Somnolence; Spinal cord compression; Syncope

PSYCHIATRIC DISORDERS - Agitation; Confusion; Delirium; Personality change; Restlessness

RENAL AND URINARY DISORDERS - Hematuria; Proteinuria

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Hypoxia; Nasal congestion; Oropharyngeal pain; Pleural effusion; Productive cough; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (hypoventilation); Sneezing; Voice alteration; Wheezing

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Pruritus; Rash maculo-papular

VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Thromboembolic event

NOTE: Larotrectinib sulfate (BAY 2757556, LOXO-101) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

3.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

Subjects who experience a clinically significant hematologic or non-hematologic AE other than nausea, vomiting, diarrhea, or dizziness due to dehydration, as defined below, at any point during the cycle should have Larotrectinib (LOXO-101) dosing held for up to 4 weeks to evaluate the AE and to allow for recovery. Clinically significant hematologic or non-hematologic AE other than nausea, vomiting, diarrhea or dizziness due to dehydration is defined as:

- Any Grade 2 AE that is more than 1 grade change from baseline AND causing intolerable symptoms
- Any Grade 3 or higher AE

Subjects may restart on treatment once the AE has recovered to grade 1 or baseline level. If the AE is considered unrelated to Larotrectinib (LOXO-101), dosing may be restarted at the same dose. If the AE is considered related to Larotrectinib (LOXO-101), then the following dose modifications should be made as in Table 3. Management of nausea, vomiting, diarrhea or dizziness due to dehydration is addressed separately in Table 4.

Table 3: Dose modification table

Event	Dose modification
1st dose reduction	75 mg BID
2nd dose reduction	50 mg BID
3rd dose reduction	Stop treatment

Subject requiring that drug be held for more than 4 consecutive weeks to recover from toxicity should be removed from therapy. Subjects who have been dose reduced due to grade 2 or grade 3 AEs, and who tolerate the reduced dose of Larotrectinib (LOXO-101) without drug-related toxicity > grade 1 may be re-escalated to a higher dose level with the agreement of the Investigator and Sponsor. If the AE that led to the original dose reduction re-occurs at grade 3 or higher after dose re-escalation, then dose should be reduced again and the reduction should remain permanent.

Regardless of dose interruptions, cycle lengths will remain 28 days and evaluations are to be performed according to the schedule in Section 4.1.

3.4.1 AEs of nausea, vomiting, diarrhea, or dizziness or dehydration that may be managed with increased supportive care should be managed as indicated in Table 4. Supportive care should include hydration and the use of anti-emetics such as 5-HT3 antagonists and/or anti-diarrheals such as loperamide as appropriate.

Table 4: Management of Nausea, Vomiting, Diarrhea, or Dizziness due to Dehydration

Severity	Management
Grade 2	1st event: Institute supportive therapy. May hold Larotrectinib (LOXO-101) if considered intolerable, or continue without dose reduction, or reduce by one dose level 2nd event: Hold Larotrectinib (LOXO-101) and maximize supportive therapy. Decrease by one dose level. 3rd event: Hold Larotrectinib (LOXO-101). May discontinue if AE is poorly controlled.
Grade 3	1st event: Hold Larotrectinib (LOXO-101). Institute supportive therapy. Restart larotrectinib (LOXO-101) with reduction by one dose level. 2nd event: Hold Larotrectinib (LOXO-101) . Maximize supportive therapy. Larotrectinib (LOXO-101) may be restarted or discontinued if dose already reduced.
Grade 4	1st event: Hold Larotrectinib (LOXO-101). Maximize supportive therapy. Larotrectinib (LOXO-101) may be restarted with dose reduction by one dose level or discontinued.

3.5 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

3.6 Duration of Agent-specific treatment

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the MATCH Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression

3.7 Duration of Follow-Up

Refer to the MATCH Master Protocol for specifics on the duration of follow-up.

4. Study Parameters

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4.1 Therapeutic Parameters for Larotrectinib (LOXO-101) Treatment

NOTE: In addition to the study parameters listed in the MATCH Master Protocol, the below parameters must also be performed for patients receiving Larotrectinib (LOXO-101) treatment.

NOTE: All assessments required prior to registration to treatment should be done ≤ 4 weeks prior to registration to Steps 1, 3, 5, 7, excluding the radiologic evaluation and electrocardiogram (ECG).

Test/Assessment	Prior to Registration to Treatment	Treatment		End of Treatment	Follow Up[F]
		Every Cycle, prior to treatment	Every 2 Cycles		
H&P, Weight, Vital signs[A]	X	X[J]			X
Performance status	X	X[J]			X
CBC w/diff, plts[B]	X	X[J]			X
Serum chemistry[B]	X	X[J]			X
Radiologic evaluation[D]	X		X[D]		X[F]
β-HCG[C]	X				
Toxicity Assessment[G]		X		X	X[F]
Pill Count/Diary[H]		X		X	
ECG[K]	X	X[I]			
Tumor biopsy and blood sample for MATCH Master Protocol[E]			X	X	

A. History and physical, including vital signs and weight at the start of each cycle (up to 3 days before start of new cycle).

B. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, creatinine, glucose, phosphorus, potassium, SGOT[AST], SGPT[ALT], sodium, magnesium and serum tumor markers (including LDH, PSA if appropriate). For eligibility purposes, participants with creatinine levels above institutional normal, Cockcroft-Gault will be used to calculate creatinine clearance. CBC w/diff, platelets and serum chemistries should be performed on cycle 1, day 1 (or up to 7 days prior), and at the start of each subsequent cycle (up to 3 days before start of new cycle). CBC with differential will be performed more frequently in patients with grade 4 neutropenia or thrombocytopenia until resolution to ≤ grade 3. CBC and serum chemistries are only required in follow-up until values return to pre-treatment levels or until progressive disease.

Rev. Add29 C. Blood pregnancy test (patients of childbearing potential) required prior to beginning treatment.

D. Disease measurements are repeated every 2 cycles for the first 26 cycles, and every 3 cycles thereafter until PD or start of another MATCH treatment step. The baseline evaluation should be performed as closely as possible to the beginning of treatment and never more than 6 weeks before registration to treatment step. For multiple myeloma patients, please refer to Section 6.4 of the MATCH Master Protocol for additional information on myeloma response criteria and the required disease assessments. Documentation (radiologic) must be provided for patients

removed from study for progressive disease. The specific radiographic tests used may include CT and/or MRI scans, as appropriate for the disease under study.

E. Additional blood specimens and/or biopsies are to be submitted from consenting patients per Section 9.3.2 of the MATCH Master Protocol. Submit at the following time points, as applicable:

- Blood specimens are to be submitted at the end of Cycle 2 (prior to start of Cycle 3 treatment). If patient progresses or treatment is discontinued prior to Cycle 3, collect the blood at that time instead. On-treatment kits for blood sample collections will be automatically shipped to sites upon registration to the treatment step.
- Screening biopsies for additional aMOI assessments after registration to appropriate screening step, if applicable (Step 2 or Step 4).
- At end of all MATCH study treatments, blood specimens and/or research biopsy after consent and registration to Step 8

Please refer to Section 4 of the MATCH Master Protocol to determine whether the patient proceeds to the next screening step or to follow-up (with a potential end of treatment biopsy for research purposes on Step 8). Samples are to be submitted as outlined in Section 9 of the MATCH Master Protocol. To order Step 2/4 Screening or Step 8 kits, complete the EAY131 Collection and Shipping Kit Order Form (See Appendix XII of the MATCH Master Protocol) and fax to 713-563-6506.

F. Every 3 months if patient is < 2 years from study entry, and every 6 months for year 3. Toxicity assessments and radiologic evaluations are not required to be done during Follow Up if progression has been previously reported; however if an adverse event occurs post treatment that meets the SAE reporting requirements, it still must be reported via CTEP-AERS, even if progression has occurred.

G. Site personnel should evaluate for toxicity and discuss treatment compliance with the patient in order to ensure the medication is taken correctly; this evaluation may be conducted by telephone or in person. The Toxicity Assessment is not required prior to Cycle 1, but is required every subsequent cycle.

H. The pill calendar will be collected at the end of every cycle. The Pill Count/Diary is not required prior to Cycle 1, but required every subsequent cycle.

I. As clinically indicated.

J. For Cycle 1, if the following tests/assessments occurred within 7 days of Day 1, they do not need to be repeated at this time point: H&P, Weight, Vital Signs; Performance Status; CBC w/diff, plts; Serum chemistry; Concomitant Medications.

K. Within 8 weeks of treatment assignment.

Rev. Add13 **5. Drug Formulation and Procurement**

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

NO STARTER SUPPLIES MAY BE ORDERED. Subjects must be enrolled and assigned to the treatment subprotocol prior to submitting the clinical drug request to PMB.

Drug Ordering: NCI supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information) The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://ctepcore.nci.nih.gov/OAOP). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam/) and the maintenance of an “active” account status, a “current” password, and an active person registration status.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of agent received from the PMB using the NCI Investigational Agent Accountability Record Form for Oral Agents available on the NCI home page (http://ctep.cancer.gov). Maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator

Investigator Brochure Availability: The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

5.1 Larotrectinib (LOXO-101) (NSC #788607)

5.1.1 Other Names: Larotrectinib

Chemical Name: (S)-N-(5-((R)-2-(2,5-difluorophenyl)pyrrolidin-1-yl)pyrazolo[1,5-a]pyrimidin-3-yl)-3-hydroxypyrrolidine-1-carboxamide hydrogen sulfate

5.1.2 Mode of Action

Larotrectinib (LOXO-101) is a small molecule, ATP-competitive, selective inhibitor of the tropomyosin-related kinase (TRK) family of neurotrophin receptors, demonstrating inhibition of all three known TRK receptors (TRKA, TRKB and TRKC). In normal tissue, activated TRK receptor signaling may stimulate cellular growth, survival and differentiation. TRK receptors are encoded by NTRK genes; NTRK1, NTRK2, and NTRK3. NTRK gene fusions appear to be oncogenic and inhibition of TRK receptors may provide benefit to patients with malignancies due to oncogenic alterations in the NTRK genes.

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5.1.3 Storage and Stability

Storage: Store capsules at room temperature below 30°C (86°F). Do not freeze.

If a storage temperature excursion is identified, promptly return Larotrectinib (LOXO-101) to room temperature below 30°C (86°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies of the intact bottles are ongoing. After opening, store bottles at room temperature below 30°C (86°F) for up to 30 days. Larotrectinib (LOXO-101) capsules may be repackaged from the manufacturer-supplied HDPE bottle into a pharmacy-supplied HDPE bottle for dispensing purposes. Instruct patients to store the prescription container away from areas of high heat and humidity.

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5.1.4 How Supplied

Larotrectinib (LOXO-101) is supplied by Bayer AG and distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI.

- 25 mg capsules are opaque white, size 2, hard gelatin capsules containing 25 mg of Larotrectinib (LOXO-101) as the free-base equivalent. The capsules contain no excipients. Capsules are supplied in 60-count or 72-count HDPE bottles with induction seals and child-resistant plastic caps.
- 100 mg capsules are opaque white, size 0, hard gelatin capsules containing 100 mg of Larotrectinib (LOXO-101) as the free-base equivalent. The capsules contain no excipients. Capsules are supplied in 60-count HDPE bottles with induction seals and child-resistant plastic caps.

5.1.5 Route of Administration

Oral. Larotrectinib (LOXO-101) may be taken without regard to food

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5.1.6 Potential Drug Interactions

In-vitro, Larotrectinib (LOXO-101) is primarily metabolized by CYP3A4. Avoid use of concomitant medications that are strong inhibitors or inducers of CYP3A4.

In vitro, Larotrectinib (LOXO-101) showed no significant direct inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 and no significant time-dependent inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6, but was a weak time-dependent inhibitor of CYP3A4. Larotrectinib (LOXO-101) showed no induction of CYP1A2, but showed some induction of CYP2B6 and did induce CYP3A4. Use caution with concomitant medications that are substrates of CYP3A4.

In vitro studies suggest Larotrectinib (LOXO-101) is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), but is not a substrate of OAT1, OAT3, OCT1, OCT2, OATP1B1 or OATP1B3. Use caution in patients who are taking concomitant medications that are strong inhibitors or inducers of P-gp and BCRP.

In vitro studies suggest Larotrectinib (LOXO-101) is not an inhibitor of transporters P-gp, BCRP, MATE1, MATE2-K, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP.

Antacid use does not significantly alter the pharmacokinetics of Larotrectinib (LOXO-101).

5.1.7 Side Effects

See Section 3.3 for side effects.

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5.1.8 Nursing/Patient Implications

Advise study participants of reproductive potential to use effective contraception while receiving study treatment and for at least 1 month after the last dose of Larotrectinib (LOXO-101).

6. Translational Studies

Please refer to the MATCH Master Protocol for information on the Translational Studies.

7. References

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Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1E: Larotrectinib (LOXO-101) /NTRK Fusions

Appendix I

Patient Pill Calendar

Pill Calendar Directions

1. Store your capsules at room temperature and away from areas of high heat and humidity.
2. Take Larotrectinib (LOXO-101) by mouth, two times a day, every day, approximately 12 hours apart. Take your scheduled doses at around the same time each day.
3. Larotrectinib (LOXO-101) may be taken without regard to food.
4. If you vomit after dosing, do not retake your dose.
5. The capsules must be swallowed whole and not chewed or crushed or otherwise manipulated.
6. If a dose is missed, only make up this missed dose if it is still more than 8 hours until the next scheduled dose.
7. Please bring the empty bottle or any leftover capsules and your pill calendar to your next clinic visit.
8. You will continue to receive the next scheduled doses as prescribed.

Patient Pill Calendar

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each capsule. **Note the times and the number of capsules that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused capsules and your completed pill calendar to your doctor's visits.

LOXO-101

DAY	Date			Time capsules taken		Number of capsules taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
	Month	Day	Year	AM	PM	AM	PM	
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
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25								
26								
27								
28								

Patient Signature: _____ Date: _____

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1E: Larotrectinib (LOXO-101) /NTRK Fusions

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Appendix II

Actionable Mutations for Sub-Protocol EAY131-Z1E

Other NTRK Fusion events not listed in the table below but identified by one of the designated outside laboratories as described in the MATCH Master Protocol will also be considered actionable mutations (aMOIs) at Level of Evidence Code 3. Please refer to Section 1.4.2 of the MATCH Master Protocol for more information.

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
NTRK1	ARHGEF2-NTRK1.A21N10	Fusion	3	NTRK Gene Fusion
NTRK1	BCAN-NTRK1.B13N11	Fusion	3	NTRK Gene Fusion
NTRK1	CD74-NTRK1.C7N10	Fusion	3	NTRK Gene Fusion
NTRK1	CEL-NTRK1.C7N7.2	Fusion	3	NTRK Gene Fusion
NTRK1	CHTOP-NTRK1.C5N10	Fusion	3	NTRK Gene Fusion
NTRK1	CHTOP-NTRK1.C5N11	Fusion	3	NTRK Gene Fusion
NTRK1	EPHB2-NTRK1.E3N9	Fusion	3	NTRK Gene Fusion
NTRK1	EPS15-NTRK1.E21N9	Fusion	3	NTRK Gene Fusion
NTRK1	EPS15-NTRK1.E21N9.1	Fusion	3	NTRK Gene Fusion
NTRK1	IRF2BP2-NTRK1.I1N10.1	Fusion	3	NTRK Gene Fusion
NTRK1	LMNA-NTRK1.L10N11	Fusion	2	NTRK Gene Fusion
NTRK1	LMNA-NTRK1.L10N12	Fusion	2	NTRK Gene Fusion
NTRK1	LMNA-NTRK1.L11N11	Fusion	2	NTRK Gene Fusion
NTRK1	LMNA-NTRK1.L2N11	Fusion	2	NTRK Gene Fusion
NTRK1	LMNA-NTRK1.L3N11	Fusion	2	NTRK Gene Fusion
NTRK1	LMNA-NTRK1.L5N10	Fusion	2	NTRK Gene Fusion
NTRK1	LMNA-NTRK1.L6N12	Fusion	2	NTRK Gene Fusion
NTRK1	MPRIP-NTRK1.M14N12	Fusion	3	NTRK Gene Fusion
NTRK1	MPRIP-NTRK1.M18N12	Fusion	3	NTRK Gene Fusion
NTRK1	MPRIP-NTRK1.M21N12	Fusion	3	NTRK Gene Fusion
NTRK1	MRPL24-NTRK1.M1N9	Fusion	3	NTRK Gene Fusion
NTRK1	MRPL24-NTRK1.M1N9.1	Fusion	3	NTRK Gene Fusion
NTRK1	NFASC-NTRK1.N20N10	Fusion	3	NTRK Gene Fusion
NTRK1	NTRK1-DYNC2H1.N17D85	Fusion	3	NTRK Gene Fusion
NTRK1	PPL-NTRK1.P12N13	Fusion	3	NTRK Gene Fusion
NTRK1	PPL-NTRK1.P22N10	Fusion	3	NTRK Gene Fusion
NTRK1	PPL-NTRK1.P22N11	Fusion	3	NTRK Gene Fusion
NTRK1	RABGAP1L-NTRK1.R14N16	Fusion	3	NTRK Gene Fusion
NTRK1	RNF213-NTRK1.R15N12	Fusion	3	NTRK Gene Fusion
NTRK1	SQSTM1-NTRK1.S2N10	Fusion	3	NTRK Gene Fusion

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
NTRK1	SQSTM1-NTRK1.S5N10	Fusion	3	NTRK Gene Fusion
NTRK1	SSBP2-NTRK1.S12N12	Fusion	3	NTRK Gene Fusion
NTRK1	TFG-NTRK1.T6N10	Fusion	3	NTRK Gene Fusion
NTRK1	TFG-NTRK1.T6N14	Fusion	3	NTRK Gene Fusion
NTRK1	TP53-NTRK1.T10N9	Fusion	3	NTRK Gene Fusion
NTRK1	TP53-NTRK1.T11N9	Fusion	3	NTRK Gene Fusion
NTRK1	TP53-NTRK1.T8N9	Fusion	3	NTRK Gene Fusion
NTRK1	TP53-NTRK1.T9N9	Fusion	3	NTRK Gene Fusion
NTRK1	TPM3-NTRK1.T7N10.COSF1329	Fusion	3	NTRK Gene Fusion
NTRK1	TPM3-NTRK1.T7N12	Fusion	3	NTRK Gene Fusion
NTRK1	TPM3-NTRK1.T7N13	Fusion	3	NTRK Gene Fusion
NTRK1	TPM3-NTRK1.T7N7.ins	Fusion	3	NTRK Gene Fusion
NTRK1	TPM3-NTRK1.T8N10	Fusion	3	NTRK Gene Fusion
NTRK1	TPR-NTRK1.T16int9N10	Fusion	2	NTRK Gene Fusion
NTRK1	TPR-NTRK1.T21N10.COSF1326	Fusion	2	NTRK Gene Fusion
NTRK1	TPR-NTRK1.T21N9	Fusion	2	NTRK Gene Fusion
NTRK1	TPR-NTRK1.T6N12.1	Fusion	2	NTRK Gene Fusion
NTRK1	TPR-NTRK1.T6N12.COSF1324	Fusion	2	NTRK Gene Fusion
NTRK2	AFAP1-NTRK2.A14N12	Fusion	3	NTRK Gene Fusion
NTRK2	AGBL4-NTRK2.A6N16	Fusion	3	NTRK Gene Fusion
NTRK2	DAB2IP-NTRK2.D1N17	Fusion	3	NTRK Gene Fusion
NTRK2	NACC2-NTRK2.N4N13.COSF1448	Fusion	3	NTRK Gene Fusion
NTRK2	NAV1-NTRK2.N15N11	Fusion	3	NTRK Gene Fusion
NTRK2	QKI-NTRK2.Q6N16.COSF1446	Fusion	3	NTRK Gene Fusion
NTRK2	SLMAP-NTRK2.S14N16	Fusion	3	NTRK Gene Fusion
NTRK2	SQSTM1-NTRK2.S5N17	Fusion	3	NTRK Gene Fusion
NTRK2	TRIM24-NTRK2.T12N15	Fusion	3	NTRK Gene Fusion
NTRK2	TRIM24-NTRK2.T12N16	Fusion	3	NTRK Gene Fusion
NTRK2	VCL-NTRK2.V16N12	Fusion	3	NTRK Gene Fusion
NTRK3	AKAP13-NTRK3.A14N14	Fusion	3	NTRK Gene Fusion
NTRK3	BTBD1-NTRK3.B4N14	Fusion	3	NTRK Gene Fusion
NTRK3	COX5A-NTRK3.C1N15	Fusion	3	NTRK Gene Fusion
NTRK3	EML4-NTRK3.E2N14	Fusion	2	NTRK Gene Fusion
NTRK3	ETV6-NTRK3.E4N14.1	Fusion	2	NTRK Gene Fusion
NTRK3	ETV6-NTRK3.E4N15.COSF823.2	Fusion	2	NTRK Gene Fusion
NTRK3	ETV6-NTRK3.E5N14	Fusion	2	NTRK Gene Fusion
NTRK3	ETV6-NTRK3.E5N15.COSF571.1	Fusion	2	NTRK Gene Fusion
NTRK3	FAT1-NTRK3.F2N7	Fusion	3	NTRK Gene Fusion

Gene Name	Variant ID	Variant Type	Level of Evidence Code	Variant Description
NTRK3	LYN-NTRK3.L8N14	Fusion	3	NTRK Gene Fusion

Molecular Analysis for Therapy Choice (MATCH)
MATCH Treatment Subprotocol Z1E: Larotrectinib (LOXO-101) /NTRK Fusions

Rev. Add13
Rev. Add25

Appendix III

Patient Clinical Trial Wallet Card

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S):

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov