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Larotrectinib (LOXO-101) for advanced solid cancers [with an NTRK1, NTRK2, or NTRK3 gene fusion]

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LAY SUMMARY

Solid tumours are abnormal masses of tissue. They may be cancerous or not cancerous. Of the cancerous types, there are different types of solid tumours which are classified according to the types of cells from which they develop. Familiar types of solid tumors are called sarcomas if starting from cells of muscle, cartilage or fat, or carcinomas when starting from cells of organs in the body. Solid tumours are distinguished from leukaemia, which arise from cells of the blood system and which have much different natural history.

Due to new technologies, rearrangement of genes in cells can be discovered which result in two normally separate genes being brought together (a fusion), which can cause abnormalities in control of cell growth leading to development of solid tumor cancers. Fusions of a family of normal genes called NTRK have been found to cause normal cells to become cancerous and can happen in cells of both adults and children. Many different solid tumor cancers have NTRK fusions. Blocking the activity of these fusions with an oral drug called larotrectinib can be a new method of cancer treatment.

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TARGET GROUP

Larotrectinib for advanced solid cancers with an NTRK1, NTRK2, or NTRK3 gene fusion

TECHNOLOGY

DESCRIPTION

Larotrectinib (LOXO-101), is a highly selective, and potent inhibitor of the tropomyosin receptor kinase (TRK) family, TRKA, TRKB, and TRKC. In normal physiology, TRK receptors help regulate processes such as pain, sensation and movement. In non-tumor tissues, TRK protein expression is restricted to tissues involved in these physiological functions. In tumor tissue, TRK protein expression is generally limited. However, tumors harboring an NTRK fusion typically have appreciable levels of TRK kinase domain expression.

The human neurotrophic tyrosine kinase receptor genes NTRK1, NTRK2, and NTRK3, which encode the TRKA, TRKB, and TRKC proteins, respectively, are oncogenes that become active and drive cancer when placed adjacent, through the molecular process of intra- or inter-chromosomal rearrangement, to expressed genes such as ETV6, EML4, LMNA, and TPM3. Oncogenic fusions such as these generally retain, at a minimum, the 3' region of NTRK encoding the full kinase domain and some 5' protein-coding sequence of an unrelated gene such as ETV6. The resulting overexpressed and constitutively active TRK fusion proteins in turn generate aberrant signaling through downstream pathways.

There are currently three on-going studies for larotrectinib. A Phase 1 dose-escalation study in adult patients with advanced cancer (Study LOXO-TRK-14001) being conducted in the United States; a Phase 1/2 dose-escalation and expansion study in pediatric patients (≥1 month of age) with advanced cancer or with primary CNS tumors (Study LOXO-TRK-15003) being conducted in the United States and Europe; and a Phase 2 basket study in patients age 12 and older with NTRK fusion-positive tumors (Study LOXO-TRK-15002) being conducted in the United States, Europe, and Asia.

There are two formulations available for patients. An oral capsule and a liquid formulation for patients unable to swallow capsules. The dose of larotrectinib selected for further evaluation in adult and adolescent NTRK fusion patients is 100 administered twice daily, with each cycle consisting of 28 days of dosing administered on a continuous basis. In pediatric NTRK fusion patients, the dose selected for further evaluation and commercialization is 100 mg/m^2 twice daily capped at 100 mg twice daily with each cycle consisting of 28 days of dosing administered on a continuous basis.

Larotrectinib does not currently have Marketing Authorisation in the EU for any indication.

At the American Society for Clinical Oncology (ASCO) meeting held in early June 2017, larotrectinib safety and efficacy data were presented from the three ongoing clinical trials. The presentation included pooled safety and efficacy data from the first 55 enrolled NTRK fusion patients with RECIST evaluable disease, on an intent-to-treat basis, across Studies LOXO-TRK-14001, LOXO-TRK-15002 and LOXO-TRK-15003These data included. Data patients with 17 different tumour types harbouring NTRK fusions. These tumour types included:

- Salivary gland
- Infantile fibrosarcoma
- Spindle cell sarcoma

- Myopericytoma
- Sarcoma, NOS
- Peripheral nerve sheath tumor
- Infantile myofibromatosis
- Inflammatory myofibroblastic kidney tumor
- Thyroid
- Colon
- Lung
- Melanoma
- Cholangiocarcinoma
- GIST
- Appendix
- Breast
- Pancreatic

INNOVATION and/or ADVANTAGES

If licensed, larotrectinib will offer an additional treatment option for solid tumour cancers with an NTRK1, NTRK2, or NTRK3 gene fusion. The company believes that the compound's selectivity will ensure maximal efficacy, while sparing structurally similar targets such as Anaplastic Lymphoma Kinase (ALK), ROS proto-oncogene 1 (ROS1), Janus Kinase (JAK) and Vascular endothelial growth factor (VEGF), thereby reducing unintentional off-target toxicities.[3]

DEVELOPER

Loxo Oncology

AVAILABILITY, LAUNCH or MARKETING

Larotrectinib was designated Breakthrough Therapy in July 2016 for treatment of unresectable or metastatic solid tumours with NTRK fusion proteins in adult and paediatric patients.[3]

Larotrectinib is a designated orphan drug in the US for the tissue agnostic indication of 'Treatment of Solid Tumors with NTRK-fusion proteins'proteins'.[3]

Larotrectinib is a designated orphan drug in the EU for soft tissue sarcoma.[3]

PATIENT GROUP

BACKGROUND

Solid tumours arise from cells originating from non-hematopoietic elements and may be characterized as an abnormal collection of cells resulting in a mass of tissue which may be benign (not cancerous) or malignant (cancerous) with the latter characterized by the risk of metastasizing to distant sites. Different types of malignant solid tumours are classified by the cell of origin, e.g. sarcomas which are cancers arising from cells of connective or supporting tissues such as bone, fat, cartilage, or muscle, and carcinomas which are cancers arising from the glandular and epithelial cells which line bodies organs. Solid tumours are distinguished from leukaemias and lymphomas which originate from cells

of the hematopoietic system and have unique natural histories requiring different treatment approaches than those typically used for solid tumor malignancies.[1]

Genomic instability is a hallmark of cells resulting in the development of a cancer. These include gene mutations, translocations, copy number alterations, deletions, and inversions of pieces of DNA or even single nucleotides. Factors, such as radiation, environmental exposures such as tobacco or faulty DNA repair processes cause genomic instability. With the recent development of more sophisticated technologies including genomic sequencing, fusions of genes can be identified in solid tumours malignancies, the discovery of which can be result in potential new targets for therapy.[8]

The human tropomyosin-related kinases (TRKs) are a receptor tyrosine kinase family of neurotrophin receptors that are found in multiple tissues types. Three classes of TRK have been described: TRKA, TRKB, and TRKC; these are coded by the *NTRK1*, *NTRK2*, and *NTRK3* genes, respectively. The TRK receptors cross the cell membrane and are called tyrosine kinase receptors which means they bind extracellular signals called ligands which cause adjacent TRK receptors to bind together (dimerize) and become catalytically active with the propagation of normal cell signalling pathways such as the PI3 kinase pathway, phospholipase C-ɣ, the Erk 1 and 2 mitogen-activated protein (MAP) kinase pathways, and the Erk5 MAP kinase pathway which stimulate cell growth, survival, and differentiation. (Rubin and Segal 2003). The TRK proteins are involved in central and peripheral nervous system development and cell function when correctly regulated.2 But the uncontrolled regulation of TRK receptors as a result of NTRK gene fusions represents an important molecular alteration with known oncogenic and transforming potential in various types of cells.[3] A growing number of genomic sequencing studies highlights the broad cancer types associated with NTRK gene fusions.[4]

CLINICAL NEED and BURDEN OF DISEASE

In 2014, there were 356,860 new cases of cancer recorded in the UK with 163,444 cancer deaths. The prevention rate of cancer sums up to 42%. Breast, prostate, lung and bowel cancers together accounted for over half (53%) of all new cancers in the UK in 2014. Fifty per cent of people diagnosed with cancer in England and Wales survive their disease for ten years or more (2010-11). Forty two per cent of cancer cases in the UK each year are linked to lifestyle factors.[5]

Results from the literature suggest that NTRK fusions in cancer are very rare. The frequency ranges from 0.5% in common tumour types such as colon, lung and breast to 90% in rare tumour types such as mammary analogue secretory carcinoma and infantile fibrosarcoma, two clinical settings where NTRK fusions appear to be pathognomonic. Based on these data, NTRK fusions appear to be widely distributed across histologically and/or anatomically defined cancer types. Thus, NTRK fusion cancer may be among the first truly genetically defined cancers, where tumour site of origin is a minor variable in the pathologic description of these cancers.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE quality standard. Suspected cancer (QS124). June 2016.
- NICE quality standard. Sarcoma (QS78). January 2015.
- NICE quality standard. Cancer services for children and young people (QS55). February 2014.
- NICE guideline. Non-Hodgkin's lymphoma: diagnosis and management (NG52). July 2016.

- NICE guideline. Suspected cancer: recognition and referral (NG12). June 2015.
- NICE cancer service guideline. Improving outcomes for people with sarcoma (CSG9). March 2006.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Paediatric Oncology. E04/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14 NHS Standard Contract for NHS Standard Service Specification Template for Cancer: Chemotherapy (Children, Teenagers and Young Adults)/ B15/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Soft Tissue Sarcoma (Adult). B12/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Teenagers & Young Adults. B17/S/a.

OTHER GUIDANCE

No other guidance was identified.

CURRENT TREATMENT OPTIONS

Treatments for solid tumor malignancies usually include alone or in combination the use of surgery, cytotoxic chemotherapy, radiotherapy cancer drugs, externally administered radiation, hormone therapy, molecularly targeted treatment, bone marrow and stem cell transplants or other treatments.[6]

Current studies suggest that immunotherapies which optimize the human antitumor response in the treatment of cancer patients may eventually replace or be used in conjunction with current standard systemic therapy approaches in the treatment in many cancer types.[7]

Studies conducted over the past decades suggest there are diagnostic and therapeutic advantages in the identification of molecular abnormalities within cancers, including fusion genes. Because molecular abnormalities often result in cancerous transformation of normal cells, these findings offer more attractive options for new therapies directed against malignant cells while sparing normal tissues. Gene fusions have now been detected in a wide array of hematologic cancers and solid tumour cancers, including sarcomas, carcinomas, and tumours of the central nervous system.

Fusions of the TRK genes represent unique molecular abnormalities identified in a variety of malignancies seen in adults and children. Inhibition of TRK with the goal of inducing cancer remission is currently the focus of the larotrectinib program. Loxo Oncology's larotrectinib (LOXO-101) is the only selective TRK inhibitor in clinical development.

EFFICACY and SAFETY

Trial	NCT02576431, An integrated analysis of efficacy and safety from three ongoing trials of the selective TRK kinase inhibitor larotrectinib
Sponsor	Loxo Oncology, Inc.

Status	Ongoing
Source of Information	Hyman et al ASCO 2017
Location	Europe (including UK),) USA, Korea, Singapore, Japan
Design	Non-randomised, parallel assignment
Participants	N=55; aged >1 month; locally-advanced or metastatic malignancy with an NTRK1, NTRK2 or NTRK3 gene fusion; received prior standard therapy appropriate for their tumor type and stage of disease, would be unlikely to tolerate or derive clinical benefit from appropriate standard of care therapy; at least one measurable lesion as defined by RECIST 1.1
Schedule	Oral capsule or liquid solution of Larotrectinib (LOXO-101) 100mg/m2 not to exceed 100mg twice daily with each cycle consisting of 28 days of dosing administered on a continuous basis
Follow-up	Clinical staging every 2 months through cycle 12, then every 3 months. Treatment to continue until disease progression, death, withdrawal of consent, or surgery resulting in complete resection with clear margins and no pathological or radiological evidence of disease. Long term follow up for subjects who discontinue study therapy, every 3 months until official study closure for date of progression (if did not discontinue for progression on study) and subsequent anticancer therapy
Primary Outcomes	Overall response rate following treatment with larotrectinib (LOXO-101) determined by independent radiology review committee and measured by the proportion of subjects with best overall confirmed response of complete response (CR) or partial response (PR) as measured by RECIST 1.1.
Secondary Outcomes	a. Overall response rate by investigator response assessment; b. Duration of response for subjects with best overall response of CR or PR by independent radiology review committee and treating investigator; c. proportion of subjects with any tumor regression as best response; d. Progression Free Survival following initiation of larotrectinib (LOXO-101) e. Overall survival, f. number of participants with treatment-related adverse events as assessed by CTCAE v4.0; g. evaluation of clinical benefit rate; i. concordance of molecular profiling of enrollment with the diagnostic test being evaluated by the Sponsor
Key Results	These three studies enrolled a total of 55 patients with NTRK fusion cancers between March 2015 and February 2017. Median age was 45 years old with a range from 0.3 years (4 months) to 76.0 years. A total of 17 different tumor types were included. Most prevalent were mammary analogue secretory carcinoma of the salivary gland (MASC), infantile fibrosarcoma, papillary thyroid cancer, colorectal carcinoma, non-small cell lung cancer, melanoma and soft-tissue sarcoma. Various NTRK fusion constructs were enrolled. As of a data cut-off date of 14 April 2017, 50 patients had evaluable disease with confirmatory data available. The overall response rate, per investigator assessment, was 76%, with 64% partial response, 12% complete response, 12% stable disease and 12% primary progressive disease. As highlighted in the ASCO presentation by Hyman, responses occurred in patients without regards to age, tumor type, NTRK fusion gene, or partner gene. Median duration of response had not yet been reached with a median follow-up of 5.8 months. The longest responder on therapy has completed 25 cycles and

	remains on therapy. Median progression-free survival has not been reached. 75% of all patients, and 93% of responding patients remain on therapy.
Adverse effects (AEs)	As of 14 April 2017, 125 patients have been treated with larotrectinib. This includes the 55 in the primary dataset, as well as 5 additional patients with NTRK fusions treated on the pediatric study, meaning 60 patients with NTRK fusion cancers have been treated. In addition, 65 patients with cancer, but who are not known to have an NTRK fusion, were treated on the two phase 1 studies. All of these patients are included in the integrated safety database. The most common adverse events reported without regards to relationship to study drug are fatigue (38%), dizziness (27%), nausea (26%), anemia (26%, and vomiting (24%). No grade 4 adverse events have been reported in any patient. Seven patients with NTRK fusion (13%) have required a dose reduction. All remain on study with tumor regression. No discontinuations for adverse events have occurred.
Expected reporting date	December 2017

ESTIMATED COST and IMPACT

COST

The cost of larotrectinib is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☒ Other: improved quality of life for carers, improved patient convenience, wider societal benefits

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☒ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☐ Other reduction in costs

☐ Other ☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

INFORMATION FROM

Loxo Oncology did not enter information about this technology onto the *UK PharmaScan* database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. *UK PharmaScan* is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use *UK PharmaScan* so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

REFERENCES

[1] Gavhane YN, Shete AS, Bhagat AK, Shinde VR, Bhong KK, Khairnar GA, Yadav AV. *Solid Tumors: Facts, Challenges and Solutions*. Vol.2 (1), 2011, 1-12. ISSN: 0975-9492.

[2] Ignyta. *Neurotrophic Tyrosine Kinase 1 – NTRK Fusions*. Available from: https://ignyta.com/providers/rx-precision-medicine-pipeline/entrectinib/ntrk-fusions/ [Accessed 31st May 2017]

[3] Amatu A, Sartore- Bianchi A, Siena S. *NTRK gene fusions as novel targets of cancer therapy across multiple tumour types*. ESMO Open 2016;1:e000023. doi:10.1136/esmoopen-2015-000023.

[4] Archer DX, Inc. *FusionPlex NTRK Kit*. Available from: http://archerdx.com/fusionplex-assays/ntrk [Accessed 31st May 2017]

[5] Cancer Research UK. *Cancer Statistics for the UK*. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics#heading-Three [Accessed 01st June 2017]

[6] Cancer Research UK. *Treatment for Cancer*. Available from: http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment [Accessed 31st May 2017]

[7] Global Data. *ASCO. Immunotherapy Combinations, Biomarker Debates, and a Big Data Clinical Database Game-Changer*. 2015. Log-in required