

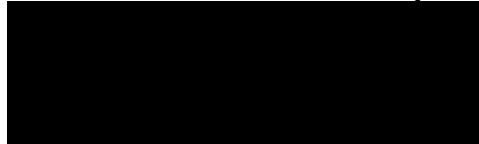


Title:

Retrospective analysis of the experience with Larotrectinib in patients with solid neoplasms with NTRK fusion in Spain (SPAINTRK)

Sponsor:

Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)



Protocol Code:

GETNE S2411 / SPAINTRK

Abbreviated title:

Experience with Larotrectinib in the Spanish population (SPAINTRK) prior to reimbursement

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Protocol version and date:

1.1, January 13th, 2025

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SPONSOR'S SIGNATURE PAGE

Study title: Retrospective analysis of the experience with Larotrectinib in patients with solid neoplasms with NTRK fusion in Spain (SPAINTRK)

Sponsor's protocol number: **GETNE S2411 / SPAINTRK**

Protocol version and date: 1.1 from January 13th, 2025

SPONSOR REPRESENTATIVE:	
_____ Full Name Title	_____ Signature date
COORDINATING INVESTIGATORS	
_____ Full Name Site Coordinating Investigator	_____ Signature date

PRINCIPAL INVESTIGATOR	
Dr.	
Principal Investigator	Signature date (dd/mm/yyyy)
Site:	

ABBREVIATIONS

ATP: adenosine triphosphate.

BDNF: brain-derived neurotrophic factor.

BSA: body surface area.

CR: complete response.

DoR: duration of the response.

DTC: differentiated thyroid carcinoma.

ECOG: eastern cooperative oncology group.

eCRF: electronic case report form.

EMA: European Medicines Agency.

EOM: estudio observacional con medicamentos.

ERK: extracellular signal-regulated kinase.

FDA: Food and Drug administration.

FISH: fluorescence in situ hybridization.

IHC: Immunohistochemistry.

MAPK: Mitogen activated protein kinase.

NGF: neurotrophins – nerve growth factor.

NGS: next-generation sequencing.

NT: neurotrophin.

NTRK: neurotrophic tyrosine receptor kinase.

ORR: objective response rate.

OS: overall survival.

PD: progression of the disease.

PFS: progression free survival.

PI3K: phosphatidylinositol 3-kinase.

PLCg: phospholipase C-g.

PR: partial response.

PT: preferred term.

PTC: papillary thyroid carcinoma.

SOC: system organ class.

Trk: tropomyosin receptor kinase.

1. PROTOCOL SUMMARY

OBSERVATIONAL POST-AUTHORIZATION STUDY

1.1. Administrative Information

Study title: Retrospective analysis of the experience with Larotrectinib in patients with solid neoplasms with NTRK fusion in Spain (SPAINTRK)
Abbreviation: Experience with Larotrectinib in the Spanish population (SPAINTRK) prior to reimbursement
Reason for developing the study: Initiative of the sponsor
Sponsor: Grupo Español de Tumores Neuroendocrinos y Endocrinos (GETNE)
Sponsor's contact address: [REDACTED]
Clinical monitor: MFAR Clinical Research S.L.
Monitor contact address: [REDACTED]

1.2. Methodological Aspects

Medical product of interest Larotrectinib
First Ethical Committee that evaluated the study: Independent Ethics Committee (IEC) of Hospital Universitario Vall d'Hebron
Coordinating Investigators Dr. Jorge Hernando
Coordinating Investigator Centers: Medical Oncology Department, Vall d'Hebron University Hospital, Vall d'Hebron Institute of Oncology, Barcelona.
Autonomous Community of the Coordinating Investigator Catalonia
Territorial scope:

Spain
Source of information: Patient medical records
Type of study (according AEMPS classification): Observational
Retrospective study: Yes
Total number of patients expected to be included: 19
Planned study duration: 12 months
Study duration for each participant: 6 months
Objectives: PRIMARY: -Description of the effectiveness of Larotrectinib treatment in tumors with NTRK fusion in Spanish patients as a clinical series. SECONDARY: -Description of treatment duration, including dose reductions and interruptions as well as the reason to do so during the treatment with Larotrectinib -Description of the effectiveness of Larotrectinib according to the previous lines of therapy -Line of treatment at which molecular testing for NTRK was performed. -Exploration of clinical or histological variables related to the effectiveness and tolerability of the treatment.
Main parameter for evaluation Effectiveness
Number of investigators (expected): A total of 14 investigators from 14 hospitals are expected to be included in the study.
Field of application: Solid neoplasms

2. BACKGROUND

2.1. Multi-omics approaches contribute to the development of new anti-cancer therapies.

In the last decade, precision medicine, using integrative multi-omics approaches, provided a new field of opportunities for developing new therapies to specifically treat each tumor type and patient (1–3). Particularly, treatment of solid tumors had a critical change in recent years, thanks to the improvement and development of these molecular diagnostic technologies that allowed to effectively identify oncogenic mutations, such as gene activation point mutations, in-frame insertions/deletions and amplification and gene re-arrangements. In addition, the identification of biomarkers by these techniques, contributed to the prediction of treatment response in cancer patients and contributed to the development of novel and effective anticancer agents, such as those known as “histology-agnostic” medication (4). Histology-agnostic drugs are based on a molecular biomarker that defines the disease and not the organ (5). This is in contrast to other traditional drugs which are developed based on tumor type or those that arise from a genomic approach based on the finding of a biomarker-defined population within a tumor type. Indeed, since 2017, the Food and Drug Administration (FDA) approved few anticancer agents with histology-agnostic indication. Some of those were related to the neurotrophic tyrosine receptor kinase (NTRK) gene fusions, NTRK1, NTRK2 and NTRK3, which are oncogenic drivers that can be targeted with these histology-agnostic inhibitors and are present in solid tumors (6).

Therefore, it seems essential the implementation of next-generation tumor sequencing as regular clinical practice for cancer patients, to identify genetic variants that will contribute to select the most effective treatment for the genetic alteration within each tumor. However, there are several methods to identify NTRK gene fusions, such as immunohistochemistry, fluorescence *in situ* hybridization and next-generation sequencing. Therefore, clinicians should select the testing method individualized to each patient (7).

2.2. NTRK fusions present in solid tumors.

More in detail, oncogenic alterations such as NTRK gene fusions, present in solid tumors, constitute an excellent target for a precise therapy specifically for these tumors, to halt its disease progression. NTRK fusions occur in the genes NTRK1, NTRK2 and

NTRK3 that encode for the TrkA, TrkB and TrkC receptors, which are the 3 transmembrane proteins with cytoplasmic tyrosine kinase domains, comprised in the tropomyosin receptor kinase (Trk) family (7). Trk signal transduction is mediated by neurotrophins-nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophins 3 and 4 (NT3 and NT4). The role of neurotrophins through activation of Trk receptors deals with regulation of cell survival, proliferation, fate of neural precursors, axon growth, dendrite pruning and patterning of innervation and the expression of proteins essential for an adequate neuronal functioning, such as ion channels and neurotransmitter receptors (8). Expression of Trk receptors after embryogenesis, is primarily restrained to the nervous system, by exerting effects on regulation of pain, proprioception, appetite and memory (9).

As previously mentioned, fusions of the tropomyosin receptor kinase (Trk) can constitute the primary oncogenic drivers in tumors that harbor them, in fact, it is very uncommon the presence of other known oncogenic alterations within the same tumor (10). Besides, NTRK gene fusions are not common in the majority of cancers, they are present in more than 90% of some rare tumors (11,12). Oncogenic fusions occur between the kinase domain of NTRK1, NTRK2 or NTRK3 and a number of N-terminal domains. These fusions consequently lead to overexpression of the chimeric protein, which results in the constitutive activation of the ligand-independent downstream signaling, that may end in an uncontrolled cell growth and proliferation, increasing the chance of cancer development (12). NTRK fusions were firstly identified in colorectal and papillary thyroid carcinomas from both adults and pediatric patients (13–16). Frequency of these fusions varies from <1% in cancer types including lung, colorectal, pancreatic, breast cancers melanoma and other solid or hematological cancers, up to 25% in thyroid, spitzoid and gastrointestinal stromal tumors and >90% in rare tumors types, specifically secretory breast carcinoma, mammary analogue secretory carcinoma, congenital infantile fibrosarcoma, and cellular or mix congenital mesoblastic nephroma (12). Interestingly, cancer types with high prevalence of NTRK fusion were largely pediatric cancers, such as Trk fusion-positive thyroid carcinoma (17,18), differentiated (DTC) or papillary (PTC) (11.5-26.09%) (19). The prevalence of NTRK fusion has been reported to be found in 1.2% of mostly non-metastatic thyroid cancers (20), in fact, papillary thyroid carcinoma, was one of the first tumor types in which the NTRK1 fusions were identified (12,21). Approximately between 5-25% of PTC cases in pediatric patients harbor NTRK fusions while 6% of adult PTCs have NTRK fusions.

These thyroid carcinomas positive for TRK fusions seem to present a unique histology pattern as a follicular growth, commonly associated with locoregional and distant metastatic disease (18,22).

2.3. Trk inhibitors for treatment of solid tumors harboring NTRK fusions.

Multiple studies reported a promising benefit of the use of Trk inhibitors for patients with solid tumors that meet certain criteria, such as the tumor must have an NTRK gene fusion and no documented resistance to the variant. Patient criteria also included metastatic disease and significant morbidity in the event of surgical resection. There must also be no adequate alternative treatment options or documented progression after previous treatment (23).

2.3.1 Larotrectinib as a Trk inhibitor.

Larotrectinib, is one of the histology-agnostic drugs previously mentioned, approved by Food and Drug Administration (FDA) and European Medicines Agency (EMA) (13,24,25). In detail, Larotrectinib is a potent and highly selective small-molecule inhibitor that binds to all three Trk (A, B and C) proteins, present in cancer cells, consequently promoting a blockage in downstream signaling for cancer cell growth. TrkA receptors interaction with NGF causes the activation of the RAS/Mitogen activated protein kinase (MAPK) pathway, which leads to increased proliferation and cellular growth through extracellular signal-regulated kinase (ERK) signaling. Other pathways such as phospholipase C-g (PLCg) and Phosphatidylinositol 3-kinase (PI3K) are also activated. TrkC coupling with NT3 causes preferential activation of the PI3/AKT pathway preventing apoptosis and increasing cell survival, whereas TrkB transduces the BDNF signal via Ras-ERK, PI3K and PLC pathway, resulting in cell differentiation and cell survival (25). Therefore, Larotrectinib specifically blocks the ATP binding site and demonstrates high potency against TrkA, TrkB and TrkC (26).

Several clinical trials provided evidence that treatment with Larotrectinib in patients with TRK fusion cancer across a diverse range of tumor types, irrespective of age, NTRK gene, or fusion partner improved clinical outcomes in those patients (13,27–30). However, it should be noted that besides the probed efficacy and the safety data collected in those trials, there is a need to monitor cognitive development in pediatric patients undergoing long-term treatment, since TRK plays an essential role in neuronal maturation and proliferation.

All those trials emphasized the critical role of screening methods to detect NTRK fusions, and recommended considering them as a priority at diagnosis in order to identify those patients who can benefit from Larotrectinib therapy.

There is a risk acquiring on-target resistance to Trk inhibitors, patients with advanced stage Trk fusion cancers and treated with Trk inhibitors may not be able to tolerate Trk inhibitor therapy and progress. Mechanisms involved in development on-target resistance can be related to amino acid substitutions in the solvent front, xDFG and gatekeeper residues in the kinase domain of Trk fusion proteins, which sterically interfere with Trk inhibitor binding. It may occur off-target or bypass resistance mechanisms that enable tumors to develop by non-TRK signaling mechanisms. However, an interesting observation is that Larotrectinib can enhance radioactive iodine uptake in advanced thyroid cancer. This is interesting since, it has been reported that differentiated thyroid carcinoma may lose their capacity to take up iodine as a consequence of oncogene activation through signaling pathways. This finding suggests that treatment with radioactive iodine may be considered in patients who receive Larotrectinib (31).

2.3.2. Sequencing methods and Larotrectinib treatment implementation in Spain.

Therefore, approval of Larotrectinib by the FDA on 26 November 2018, constituted an important milestone in the context of oncology and particularly in the field of treating solid neoplasm that harbors an NTRK gene fusion. Currently more and more centers perform sequencing methods (i.e, next-generation sequencing (NGS)) on their cancer patients, prioritizing certain pathologies such as thyroid or lung cancer. Spain is starting but slowly implementing NGS as a general clinical option to characterize and classify tumors in order to search for the best treatment. In fact, difficulties such as the fragmentation of Spanish healthcare and the transfer of its management to every region adds an additional difficulty.

In this scenario, the availability of data regarding safety and efficacy of treatment with Larotrectinib in a population of different neoplasms in Spain would be of relevance.

Currently, around 20 patients have received this treatment in our country (12 patients have been treated more than one year), but there is no systematic collection of data on outcomes. Therefore, this study will contribute to the understanding by clinicians and authorities that selection of the best line of treatment can be achieved by performing

NGS on patient samples, and therefore its implementation should be enhanced/reinforced in Spanish healthcare centers. The multidisciplinary oncological cooperative group GETNE, the Spanish taskforce of neuroendocrine and endocrine tumors, one of the populations especially enriched in NTRK fusions, propose the SPAINTRK observational retrospective study to reunite data from all patients treated with Larotrectinib for solid neoplasm in Spain. Therefore, GETNE will contribute and shed light on the field of therapies for tumors harboring NTRK fusions, specifically using Larotrectinib as main and an effective drug of treatment.

3. RATIONALE AND OBJECTIVES

SPAINTRK aims to be the first trial in Spain to systematically collect data on outcomes of Spanish patients with solid neoplasms treated with Larotrectinib through the compassionate drug use program, during the time elapsed between the indication approval and the drug commercialization. This will contribute to selection of the best treatment for cancer patients with NTRK fusions, such as Trk inhibitors like Larotrectinib. Since the FDA and the EMA approved the use of Trk inhibitors, like Larotrectinib, there is a new and effective option of treatment for patients with NTRK fusions in solid neoplasms. This observational retrospective study will allow to analyze data of patients treated with Larotrectinib across the country and increase the knowledge on response to rare and different cancers

3.1. Main Objective

- Description of the effectiveness of Larotrectinib treatment in tumors with NTRK fusion in Spanish patients as a clinical series.

3.2. Secondary Objectives

- Describe treatment duration, including dose reductions and interruptions occurred along the treatment with Larotrectinib, as well as to study the reasons behind those decisions.
- Study the effectiveness of Larotrectinib and previous lines of therapy.
- Identified the line of treatment at which molecular testing for NTRK was performed.
- Exploration of clinical and/or histological variables related to the effectiveness and tolerability of Larotrectinib treatment.

4. RESEARCH METHODS

4.1. Study design

This is an observational retrospective study including thyroid cancer patients with solid neoplasms with NTRK fusions.

The study will use secondary data retrieved from medical records from each patient. The medical records include all the clinical variables defined in order to perform the analysis and it is not necessary to access additional sources.

The assignment of a patient to a specific therapeutic strategy has been already decided in advance by the usual clinical practice of medicine; the decision to prescribe a specific treatment was clearly dissociated from the decision to include a patient in the study. No intervention will be applied to patients, either diagnostic or follow-up, other than the usual clinical practice. Epidemiological methods will be used to analyze the data collected.

4.2. Setting and study population

In total, 19 patients diagnosed with solid neoplasms that have been confirmed to bear NTRK fusions in their tumors will be included in the study. It is known that these patients have received the treatment with Larotrectinib in 14 centers in Spain, prior to treatment reimbursement in Spain.

4.3. Inclusion Criteria

1. Infant and adult patients (all ages).
2. Patients with confirmed diagnosis of solid neoplasms.
3. Patients must have detected NTRK fusions by the following diagnostic methods NGS, fluorescence *in situ* hybridization (FISH) and/or Immunohistochemistry (IHC).
4. Patients must be treated with Larotrectinib under the compassionate use program (before the commercialization) in order to be included in the study.
5. Data should be available in order to evaluate effectiveness and consequent follow up.

4.4. Exclusion Criteria

- Patients with solid neoplasms treated with Larotrectinib in clinical trials or other settings different from clinical practice.
- Patients that initiated treatment with Larotrectinib after the obtention of prize-reimbursement and commercialization.

4.5. Study Size

The sample size calculation is based on the actual number of patients known to be treated in Spain with Larotrectinib. At the moment 19 patients from 14 different healthcare centers have been localized that were treated in the Spanish territory with Larotrectinib. We expect to include and collect data from all of them.

4.6. Sampling and recruitment method

Patients will be consecutively included, in compliance with the previously established inclusion criteria.

According to the definition of study population and disease established in this scientific report, patients will be selected from cases diagnosed with solid neoplasms bearing NTRK fusions detected by any of these methods, NGS, FISH and/or IHC, and treated with Larotrectinib. The 19 patients treated with Larotrectinib in the Spanish territory are localized and belong to 14 different sites/healthcare centers.

To prevent two or more reporting physicians from logging the same case, a coordinator, who controls the cases included in his or her center, is appointed in health centers with several reporting physicians, and preventive measures are implemented in the tool controlling duplications in variables (such as birth date, gender, center or diagnosis).

4.7. Case Definition

A 'case' is defined as any patient, diagnosed, treated, or followed in the different health centers where reporting physicians authorized by the sponsor, who meets the inclusion criteria. A key point is that the patient was diagnosed with solid neoplasms that harbors a NTRK fusion and he/she was receiving treatment with Larotrectinib. Data from

patient's treatment should have been recorded and be available at the centers.

4.8. Data Logging

Once the patient is compliant with inclusion/exclusion criteria information on the clinical history will be collected to gather the necessary data and to complete the electronic forms of the study designed for this purpose. All data collected during treatment, as well as demographic data, will be provided for the purpose of this study and completed at the electronic Case Report Form (eCRF) to proceed to its analysis.

4.9. Study Calendar

Start date of data collection (*First Patient First Visit of Data Extraction Start*): January 2025 (expected).

End of data collection (*Last patient Last visit or data extraction completion*): May 2025 (expected)

Completion of Study Report: 4Q 2025 (expected)

Primary publication date: 1Q 2026 (expected)

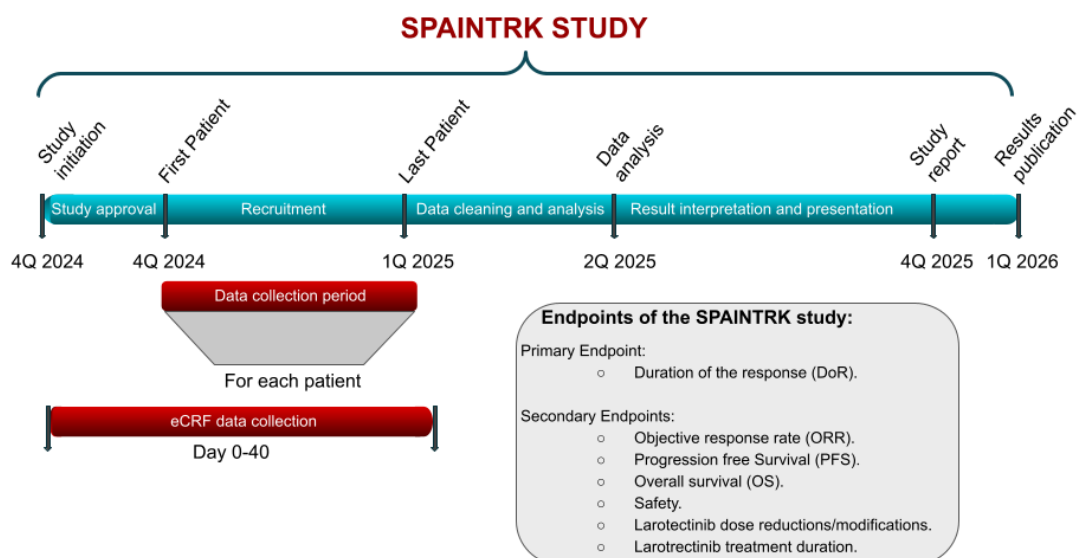


Figure 1. Study calendar scheme and milestones.

5. ENDPOINTS AND VARIABLES

5.1. Endpoints

5.1.1. Primary Endpoints

- Duration of response (DoR): is defined as the time from first confirmed response (complete (CR) or partial (PR) response), according to Objective response rate (ORR) defined below, to the date of the documented progression of the disease (PD) as determined using RECIST V1.1 criteria or death due to any cause, whichever occurs first. Those patients with response and without PD or death event will be censored on the date of their last tumor assessment.

Results will be presented as individual cases, not compiled as the patients have different pathologies which may differ in prognosis.

5.1.2. Secondary Effectiveness Endpoints

- Objective response rate (ORR): is assessed by the investigator analysis of tumor growth through imaging follow-up (CT scan/MRI), using a method to evaluate it as RECIST V1.1. This will be considered as the number of patients with confirmed complete response (CR) or partial response (PR) as their overall best response throughout the period of treatment with Larotrectinib. Tumor measurements that were assessed locally by the clinician according to RECIST, V1.1, should be recorded and indicate the change in size of tumors as compared with baseline, at the first dose of study treatment.
- Progression free survival (PFS): Time from first dosing date to the date of confirmed PD according to RECIST 1.1. Patients alive and free of events at the date of the analysis will be censored at their last known tumor assessment. Patients who start a new treatment line without progression will be censored on the date of first dose of the subsequent anticancer treatment.
- Overall survival (OS): defined as the time elapsed from the first dose of study treatment until death from any cause. Patients alive and free of events at the date of the analysis will be censored at their last known contact. Survival will be assessed by recording patients' status at each visit.

Results will be presented as individual cases, not compiled as the patients have different pathologies which may differ in prognosis.

5.1.3. Secondary Safety Endpoints

- Safety: All safety information will be collected retrospectively according to data available in the chart review. A descriptive analysis of adverse events collected in medical charts will be done taking into account:
 - The frequency of AEs will be reported per patient by MedDRA System Organ Class (SOC) and Preferred Term (PT);
 - The maximum CTCAE grade will be reported per patient;
 - The causal relationship with the study drug will be assessed locally by the investigator
- Larotrectinib interruptions / Delays: number of interruptions and delays of EB treatment reported per patient (frequency) and reason for dose interruption / delay.
- Larotrectinib dose reductions or modifications: Number of reductions or modifications of EB doses reported per patient (frequency) and reason for dose reduction / modification.
- Larotrectinib treatment duration: Time elapsed between first dose and permanent discontinuation of the study treatment.

5.2. Study Variables

Investigators will provide information of each of the following variables:

- Variables for Demography:
 - Age at enrollment.
 - Sex (male, female).
 - Race (white, black, Asian, other)
 - Height (cm).
 - Weight (kg).
 - Body mass index.
 - Body surface area (BSA) - calculated from the reported height and weight using Mosteller's formula:
 - $BSA (m^2) = (\text{height (cm)} \times \text{weight (kg)} / 3600)^{1/2}$
 - Performance status will be presented using the Eastern Cooperative

Oncology Group (ECOG) scale.

- Cancer history:
 - Primary cancer diagnosis.
 - Primary tumor type, histology and location
 - Stage of disease at initial diagnosis(I-IV).
 - Time since initial diagnosis.
 - Extent of disease at enrollment (metastatic, locally advanced, sites of disease, presence of at least one measurable lesion). Stage of the disease at inclusion
 - Time since diagnosis of metastatic or locally advanced disease (years).
- Prior anticancer treatments:
 - Prior systemic treatments type, start and end dates.
 - Number of prior systemic regimens or treatment courses.
 - Best overall response to the most recent prior systemic regimen or treatment course (CR, PR, stable disease, progressive disease, unknown or inevaluable or not applicable).
 - Prior radiotherapy.
 - Prior cancer-related surgery.
- NTRK fusions:
 - NTRK fusion gene: NTRK1, NTRK2, NTRK3.
 - NTRK fusion isoform (i.e ETV6-NTRK3).
 - Method of detection: NGS, FISH or IHC and dates of the determinations.
 - Other oncogenic alterations present.
- Treatment with Larotrectinib:
 - Dose of Larotrectinib.
 - Larotrectinib start and end date. Reasons for end of treatment
 - Data records of dose reductions and/or interruptions and their reason.
 - Best response and best response date
 - Progression date.
 - Frequency of AEs reported per patient by MedDRA System Organ Class (SOC) and Preferred Term (PT); the maximum CTCAE grade will be reported per patient. Causal relationship with the study treatment will be

reported for all events.

- Survival:
 - Patient status (alive, death, lost to follow-up)
 - Reasons of death (if applicable)
 - Subsequent anticancer treatments (type, start and end dates, best response, progression dates)

6. PROTECTION OF HUMAN SUBJECTS

6.1. Applicable Legislation

This is an observational, descriptive, non-interventional study with the main objective of collecting information on Larotrectinib-treated solid neoplasms patients with detected NTRK fusions, under clinical attention and follow-up in oncology departments of centers distributed across national level.

The study design includes retrospective data collection. Therefore, in accordance with the Royal Decree 957/2020 which regulates the observational studies with medicines for human use, this is considered a retrospective observational study with medicines (Estudio observacional con medicamentos [EOM]). In compliance with the same legislation, the participation of any center will be conditional upon approval of a Clinical Research Ethics Committee and/or authorization through the institution conformity.

Participating in this study does not pose any additional risk to patients because this is a study developed from information retrieved from the clinical histories and clinical assessment of patients, all in the context of the usual clinical practice and without the involvement of patients in any type of intervention or without the modification of the treatment that they would receive had they not participated in the study.

The present protocol will be conducted in accordance with the principles adopted by the 18th World Medical Assembly (Helsinki, 1964) and their subsequent amendments (Fortaleza, 2013), following the rules of good clinical practice and deontological code.

6.2. Oversight Clinical Research Ethics

The study will be initially submitted for evaluation by the Clinical Research Ethics Committee of the Hospital Vall d' Hebron (Barcelona). As detailed in section 6.1, the study will also have the corresponding and applicable authorisations according to the local regulations of each center and the guidelines of the Royal Decree 957/2020 which regulates the observational studies with medicines for human use.

6.3. Informed Consent

Patients will not be asked for informed consent to be registered as a case in this study. This study is considered to meet all the requirements for exemption from consent according to the "International Ethical Guidelines for Health-related Research Involving

Humans” (CIOMS-OMS 2016):

- This is a study of general public interest and social value, in the field of biomedical research.
- It is a case registry in which the retrospective collection of personal and health data of the patient is minimized to the maximum, which is kept in a secure system with access restricted exclusively to the researchers of the participating hospital and the coordinators of the study.
- Obtaining informed consent for this registry may be impractical in many cases, due to the acute or serious condition of the patient and the moment in which the oncologist becomes aware of the case. Additionally, obtaining consent would be a limitation for the correct execution of the project, which requires an exhaustive registry of all cases of which there is knowledge.
- Finally, it is considered that the collection of cases with the established confidentiality guarantees does not pose any risk to patients.

The patient's participation in the study must be recorded in the patient's medical history, making explicit reference to the study SPAINTRK / GETNE S2411.

The sponsor's objective is to avoid serious problems of scientific validity that could mean that a relevant proportion of patients are lost, for example those with fatal events or loss of follow-up, and that due to a lack of representativeness of the population affected by the disease, the results obtained may present some type of bias.

For all patients, the data are included in the study in an anonymized and dissociated form, guaranteeing that they cannot be associated with any identified or identifiable person. The use of patient data will be subject to a commitment of confidentiality by all personnel participating in the study, including the researcher and his collaborators, data managers, data analysts, and monitors; this must be correctly recorded in the patient's medical history, with specific reference to the study SPAINTRK / GETNE S2411.

6.4. Confidentiality

Pursuant to the Statutory Law on Personal Data Protection (*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos de Carácter Personal y garantía de los derechos digitales* – LOPD), the sponsor guarantees the adoption of necessary measures to ensure the confidential treatment of personal data.

Only reporting physicians will know the full name of their patients. No sensitive

information unnecessary for the intended purposes of the study is collected.

An electronic platform will be used to log data in the eCRF. To access the application, users must identify themselves with a username and a password strictly for personal use. Each reporting physician will only access the data he or she introduced that is strictly necessary for the job. Any document containing identifying data of the principal investigator, hospital, contact person, and telephone number will remain in the center at all times, without being included in the database.

Data will be collected in a research file under the responsibility of the sponsor and will be treated in the framework of the study, guaranteeing that the sponsor will adopt pertinent measures to ensure compliance with the current legislation on data protection in all cases. The coded data can be transmitted to third parties and to other countries but in no case they will contain information that can directly identify any patient, such as name and surnames, initials, address, or social security number, among others. If this transfer occurs, it will be for the same study purposes as those described above or for scientific publications only, but always maintaining patient confidentiality according to current legislation.

The database will be examined exclusively by the scientific and medical staff of the sponsor. No personal data or any information that may be related to patients will be included in this database. The database administrator, treatment manager, and monitor (if applicable) will have access to all data that are not linked to any identifiable person.

In data explorations by researchers authorized by the Scientific Committee and in international data transfers to International Registries, if applicable, patients will be identified by a numerical code automatically and randomly assigned by the computer application at the start of logging of each case to maintain the confidentiality of personal patient data, as established in the European Union (EU) Parliament and Council General Data Protection Regulation 2016/679 on April 27, 2016. This type of coding is used because it guarantees patient confidentiality while respecting the exercise of their access, revocation, consultation, and opposition rights.

Access to personal information of the study subjects will be restricted to the study physician/collaborators, health authorities (Spanish Medicines Agency), Clinical Research Ethics Committee, and staff authorized by the sponsor, when they need to assess study data and procedures, but always maintaining patient confidentiality in compliance with the current legislation.

This assessment will be performed in the presence of the principal investigator or

collaborators, responsible for guaranteeing the data confidentiality on the clinical histories of the study subjects. Only data collected for the study will be transmitted to third parties, which in no case will contain information that can directly identify the study subjects, such as name and surnames, initials, address, or social security number, among others. If this transfer occurs, it will be for the same study purposes as those described here and maintaining patient confidentiality, at least with the level of protection of the current legislation, including data transfer outside the area of application of the reference legislation.

6.5. Funding Source

The study sponsor, GETNE through collaboration with Bayer Hispania S.L.U, funds the study according to the guidelines of the present protocol. This funding covers the cost of registration and control processes in Ethics Committees and health authorities; the design, maintenance, and management of the database; eventual statistical consultations, if necessary; and publishing and reporting costs. The funding will be, in any case, independent of the results of the study.

The sponsor guarantees non-interference in the processes of case selection, data analysis, or in any other process that may affect the study results involving data exploration and presentation.

6.6. Potential advantage and limitations of research methods

The observational approach of this study offers the advantage of generating scientific data to demonstrate that detection of NTRK fusion in patients with solid neoplasms by using detections methods such as NGS, FISH or IHC in the real world and give external validity to the clinical trials that led to its commercialization. Accordingly, this study will assess whether treatment with Larotrectinib supposes an effective benefit on these patients.

Inherent limitations of non-interventional, observational studies in general are the risk of selection/ascertainment bias, the inclusion of non-standardized assessments and evaluations, the non-standardization of time-points, and the lack of a parallel control group, which complicate the interpretation of the causality between treatments and outcomes. Furthermore, as with any "as observed" analysis, there is a potential risk of bias due to missing outcome data; this specific risk increases with the number of missing outcome data.

7. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

As stipulated in the Royal Decree 957/2020 which regulates the observational studies with medicines for human use, for those studies in which detection of suspected serious adverse reactions during the study is not possible or where the individual evaluation or causality of a clinical event within an specific drug is not appropriate (such as those retrospective), expedite notification of suspected adverse reactions will not be mandatory.

Accumulated data on safety aspects (serious adverse events and adverse drug reactions) related to medical products subject of study will be recorded by sites in the eCRF and included in the clinical study report by the sponsor, as this study is based on secondary use of data, no expedite reporting to the Sponsor is required.

In addition to the details specified in the previous paragraph, any relevant safety finding detected during the study will be brought to the attention of the AEMPS and competent bodies of Autonomous Communities involved, regardless of the study design or type.

8. QUALITY ASSURANCE

8.1. Control of data consistency

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data.

- The study will use eCRFs. A designated CRO staff will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the findings and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.
- Concomitant treatments and all information on medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system.
- Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.
- The site staff designated by the investigator will enter the information required by the protocol onto the eCRFs as well as onto the designated CRO's requisition form.

8.2. On-site quality control

- Before study initiation, the protocol and eCRFs will be reviewed with the investigators and their staff through a telephonic site initiation visit.
- During the study, a monitor will contact the selected sites through remote monitoring visits to check the completeness of patient records, the accuracy of entries on the eCRFs. Key study personnel must be available to assist the field monitor during these visits.
- The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments.
- All information recorded on eCRFs must be traceable to source documents in the patient's file.

- The investigator must give the monitor access to all relevant source documents to confirm their consistency with the eCRF entries.

8.3. Audits

- To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the “Sponsor” may conduct site visits to institutions participating in protocols.
- The investigator, by accepting to participate to this protocol, agrees to cooperate fully with any quality assurance visit undertaken by third parties, including representatives from the “Sponsor”, national and/or foreign regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorized individuals.
- The investigator must inform the “Sponsor” immediately in case a regulatory authority inspection would be scheduled.
- The source documents should be stored for 5 years and be available for audits and inspections if applicable.

9. WORK PLAN (TASKS, MILESTONES AND STUDY CHRONOLOGY)

2024 (Month)	1	2	3	4	5	6	7	8	9	10	11	12
Study activation												
Recruitment period												
Data and endpoint capture												
2025 (Month)	1	2	3	4	5	6	7	8	9	10	11	12
Recruitment period												
Data and endpoint capture												
Analysis of results												
Management and presentation of data for publication												

Figure 2. Working plan and calendar, GANTT chart

Please refer to section 4 for further detail on the study calendar.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study sponsor holds the rights of exploring the data collected, stores and safeguards them, and acts as a Scientific Committee for the approval of proposals for data exploration and publication of results made by researchers.

The objective of the study, openly epidemiological, is to collect information on the management of the study disease in different participating hospitals to establish a framework for action (usual practice) and, therefore, study options for disease management beneficial for the patients.

10.1. Commitment and Publication Rules

The Coordinating Investigators and the Sponsor are responsible for the periodic preparation of monographs or manuscripts summarizing the logged data for publication. The global data will be used in papers submitted for publication to congresses and to medical journals, mentioning the study and the sponsor.

The authors of the scientific communications will be all investigators contributing to the study.

The manuscript containing the main data of this study will be submitted to a scientific, indexed, peer-reviewed journal for publication approximately 12 months after the study initiation (estimated 4Q2025). We expect to have the results published by 1Q2026 (estimated).

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APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	1.0	15 OCT 2024	List of all participating sites and physicians
1	1.0	15 OCT 2024	eCRF Template