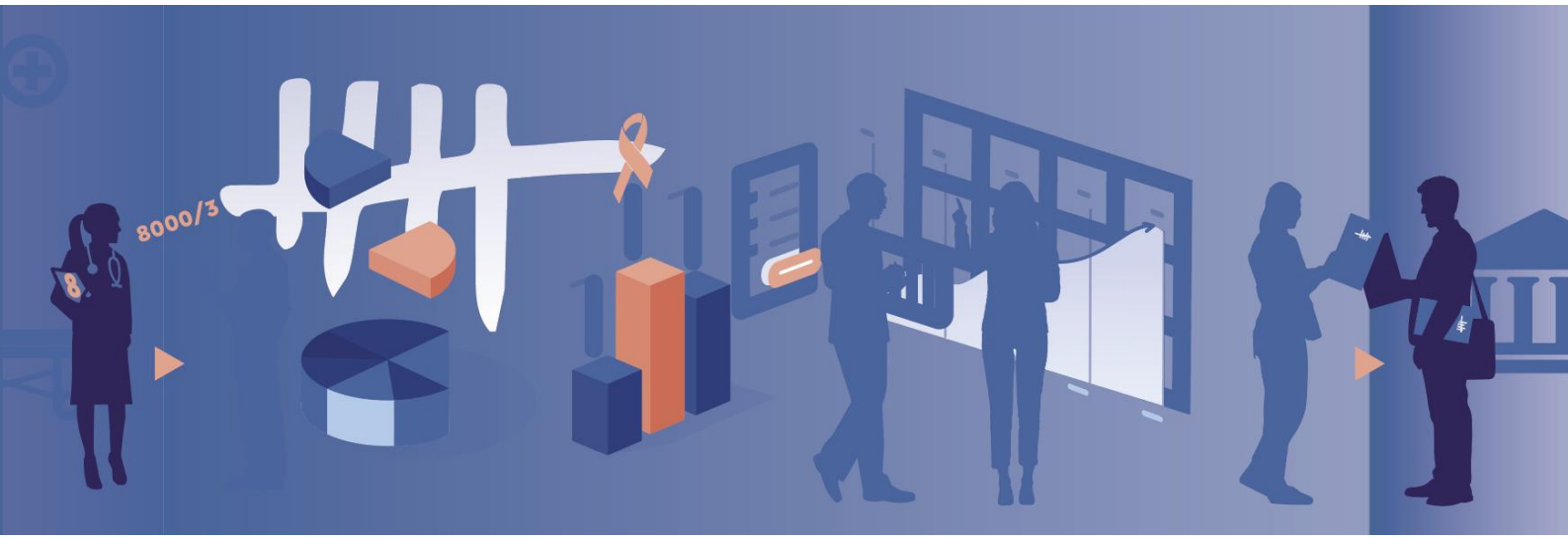
Belgian Cancer Registry

NTRK-inhibitor

Project manual + FAQ

AUGUST 2023



Contents

1. General project information

This manual has been composed as a guide and reference for filling out the specific registration form for the registration of patients receiving NTRK-inhibitor treatment.

Starting from 01/04/2021 and 01/10/2021, there is a **reimbursement of respectively Larotrectinib and Entrectinib** by the National Institute for Health and Disability Insurance (RIZIV/INAMI). Larotrectinib and Entrectinib are used for the treatment of adult and/or paediatric patients with locally advanced or metastatic solid tumours with a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion that cannot be treated satisfactorily with the available treatment options. The reimbursement is coupled to a compulsory registration of tumour and outcome-specific variables via the Belgian Cancer Registry (BCR). More information and all relevant documents can be found on the BCR website (Dutch/French).

The registration consists of 3 registration forms:

- The primary registration form: This form should be filled out at the latest 1 month after the eHealth application of the NTRK-inhibitor treatment. This form contains information until right before the start of the NTRK-inhibitor treatment.
- The follow up registration form – end of treatment: This form should be filled 6 months after the end of the NTRK-inhibitor treatment. This form contains information until 6 months after the end of the NTRK-inhibitor treatment.
- The follow up registration form:
    - This form should be filled out for **Larotrectinib** at the latest on 01/10/2023. This form is intended to collect data for the revision of the reimbursement of Larotrectinib which will start on 01/04/2023. Therefore, data collection is required from the start of the treatment until 15/09/2023 if treatment is still ongoing at that time.
    - This form should be filled out for **Entrectinib** at the latest on 01/04/2024. This form is intended to collect data for the revision of the reimbursement of Entrectinib which will start on 01/10/2023. Therefore, data collection is required from the start of the treatment until 15/03/2024 if treatment is still ongoing at that time.

All **questions** concerning the variables to be registered, registration procedures or registration deadlines can be directed to NTRKinhibitor@kankerregister.org or 02/250 10 10.

1.1. Patient inclusion criteria

The requirements for patient inclusion can be translated into the following concrete inclusion criteria for registration:

- patients with a Belgian health insurance
- have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation
- tumour is locally advanced or metastatic, or surgical resection is likely to result in severe morbidity
- have no satisfactory alternative treatments
- after approvement at a multidisciplinary oncological consult (MOC)
- for whom NTRK-inhibitor treatment is requested and approved through the eHealth platform.

The **start date of reimbursement of Vitrakvi® (Larotrectinib) and Rozlytrek (Entrectinib)** is **1/04/2021 and 1/10/2021 respectively**. All patients for which the **date of the eHealth approval**, falls on or after 01/04/2021 are included in the target population and must be registered.

Patients who are already treated with Larotrectinib or Entrectinib before respectively 01/04/2021 and 01/10/2021 as part of a Compassionate Use Program and who met the conditions stated above before the start of the treatment, also have to be registered.

1.2. Mode of registration

The registrations can be delivered to the BCR via the online **WBCR** application.
The online Web Based Cancer Registration (WBCR) application of the BCR can be accessed via the BCR website. More information about the login procedure and general operation of this application can be found in the NTRK-inhibitor WBCR manual.

Notes:

- Access to WBCR is granted via the **(Main) Access Administrator of your hospital**.
- The login procedure is via the eHealth platform. You will need your electronic identity card and PIN code. Alternatively, you could use the 'itsme app'.
- It is possible to save and modify (in)complete registrations at any time, before sending them to the BCR. After sending, the registrations can no longer be modified. The registrations can be delivered to the BCR one by one or altogether. The data you have access to, can be downloaded into a CSV file. Please check FAQ 3.1.12 to see how corrections can be sent to the BCR afterwards.
- Quality control checks have been added to the online registration form, e.g. to ensure that the dates are filled out chronologically. Possible errors need to be resolved before the registration can be validated and delivered to the BCR.
- Please keep in mind to save a registration within the hour. After staying on the same WBCR page for more than 1 hour, you will be logged off automatically and unsaved data will be lost.

1.3. Registration delivery

1.3.1. Larotrectinib

The start date of the 3-year convention is 1/04/2021; the end date is 01/04/2024. All patients within the target population should be registered if the date of eHealth approval falls on or after 01/04/2021.

There are different registration time points:

- At the start of the treatment: the primary registration form must be completed at the latest 1 month after the eHealth application of the larotrectinib treatment.
- At the end of the treatment: the follow-up registration form must be completed 6 months after the end of the Larotrectinib treatment
- On 01/10/2023: the follow-up registration form must be completed at the latest on 01/10/2023. This is only the case if treatment is still ongoing on 15/09/2023.

1.3.2. Entrectinib

The start date of the 3-year convention is 1/10/2021; the end date is 01/10/2024. All patients within the target population should be registered if the date of eHealth approval falls on or after 01/10/2021.

There are different registration time points:

- At the start of the treatment: the primary registration form must be completed at the latest 1 month after the eHealth application of the entrectinib treatment.
- At the end of the treatment: the follow-up registration form must be completed 6 months after the end of the entrectinib treatment
- On 01/04/2024: the follow-up registration form must be completed at the latest on 01/04/2024. This is only the case if treatment is still ongoing on 15/04/2024.

2. Primary registration form

The primary registration form must be filled out at the latest 1 month after the eHealth application of the NTRK-inhibitor treatment. This form contains information until right before the start of the NTRK-inhibitor treatment.

The following types of variables are used in the project:

- Date: 8 digits: 2 for the day, 2 for the month, 4 for the year (dd/mm/yyyy)
- Decimal (DEC): decimal number, can contain 1 decimal; a point '.' should be used as decimal separator
- Formatted text (FT): variable that has a specific format. For example, histology (XXXX/X) or topology (CXX.X)
- Single select (SS): Only 1 option can be chosen out of a limited selection list. This variable is indicated by the following symbol on the primary registration form: ❍
- Multi select (MS): Multiple options can be chosen out of a limited selection list. This variable is indicated by the following symbol on the primary registration form: ❒
- Number (NUM): integer number

All variables are 'necessary' variables (mandatory to be filled out) unless stated otherwise (e.g. denoted by 'if possible' or 'if applicable'). **It is strongly encouraged to fill out the free text fields in English as much as possible.**

2.1. Administrative patient data

For each new registration, the administrative patient data needs to be provided. If no INSZ/NISS number is available, the postal code, city and country must be provided.

Important remark: Only patients with a Belgian health insurance are eligible for reimbursement!

2.2. Administrative treatment data

Please provide the eHealth notification number which is the number you received when applying for NTRk-inhibitor treatment approval via the eHealth platform.
In addition, the name of the requesting physician must be filled in as well as the type of NTRK-inhibitor.

2.3. Disease information at diagnosis primary tumour

Name variable	Type	Answer options
Incidence date primary tumour	Date	(dd/mm/yyyy)
Localisation primary tumour	SS + text	Bladder
		Breast
		Cervix
		Colon
		Head and neck
		Kidney
		Lung
		Melanoma
		Oesophagus
		Pancreas
		Prostate
		Rectum
		Soft tissue
		Uterus
		Unknown
		Other, please specify …
Laterality primary tumour	SS	Left
		Right
		Unpair organ
		Unknown
Histological diagnosis primary tumour	FT	Xxxx/x

The **incidence date of the primary tumour** is the date of the first diagnosis of the primary tumour. This is the date of (with decreasing priority):

1. First microscopic (histological/cytological) confirmation of the tumour
    a. Date of biopsy/cytology procedure
    b. Date of receipt of the biopsy/cytology by the pathologist
    c. Date that protocol was written by the pathologist
2. First positive genetic/molecular test to diagnose the malignancy
3. First hospitalisation for the tumour
4. First consultation for the tumour (when there was no hospitalisation)
5. If not 1, 2, 3 or 4: Date of:
    a. First positive tumour marker test for this malignancy
    b. First imaging performed for this malignancy (incl. PET, CT, MRI)
    c. First MOC for this malignancy
6. Date of death

The following principles are kept in mind:

- The incidence date cannot be after the date of the first treatment
- Please provide the **exact date** of diagnosis for this variable! Whenever the date is unknown, e.g. in case of a referred patient, the expert center should undertake the necessary steps to determine the exact date of diagnosis, e.g. by calling the referring hospital.

The primary tumour localisation is the organ or tissue ('exact' location) where the tumour originated (this is not the location of metastasis).

The **laterality** of the primary tumour only must be specified for paired organs and is important in the context of multiple tumours. Laterality is especially important for tumours of the breast, kidney, lung, skin, bone and soft tissues. A list of paired organs can be found here.
The **histological diagnosis of the primary tumour** (format XXXX/X) gives information about the cell type of the tumour and consists of 4 characters, ranging from 8000 to 9993 (histology), followed by / and 1 character which ranges from 0 to 3 (behaviour).

- The histology code is determined by examining the cells or tissue, preferably by microscopy. When a biopsy or surgery is performed, await the results of the microscopic examination. When no anatomopathological examination is performed, the code needs to be consistent with the basis of diagnosis (e.g. basis of diagnosis 6 or 7 rarely makes it possible to use a specific histology code, exceptions are possible).
- The behaviour indicates the degree of invasiveness of the tumour. When a histological component is present within the tumour but showing a different index of behaviour, choose the highest index of behaviour. The following possibilities can be selected:
    - 0 = Benign
    - 1 = Borderline (or uncertain if malignant potential or low malignant potential)
    - 2 = Malignant, in situ (or intra-epithelial carcinoma or high-grade dysplasia)
    - 3 = Malignant, invasive

If behaviour 0 (benign) or 1 (borderline) gives a warning, please specify a validation comment: 'Histological diagnosis is correct.'

If you cannot find the correct histological description or code, please use '8000' and specify further in the comment field. The histology is coded according to the ICD-O-3 (starting since incidence year 2002). For every tumour from 01/01/2020, the new ICD-O-3.2 update has to be used (see http://www.iacr.com.fr/index.php?option=com_content&view=article&id=149:icd-o-3-2&catid=80&Itemid=545)

2.4. Gene information

Name variable	Type	Answer options
Has the patient been tested positive for NTRK gene fusion	SS	Yes*
		No
* Which NTRK gene?	SS	NTRK1
		NTRK2
		NTRK3
* Prescreening with Immunohistochemistry (IHC)?	SS	Yes °
		No
° Select test type(s):	MS	Polymerase Chain Reaction (PCR) †
		Next-generation sequencing (NGS) §
		Fluorescence in situ hybridisation (FISH) $
† Date PCR	Date	(dd/mm/yyyy)
§ Date NGS	Date	(dd/mm/yyyy)
$ Date FISH	Date	(dd/mm/yyyy)

The next question is if the patient has been tested positive for a NTRK gene fusion. Only patients with a NTRK gene fusion are eligible for reimbursement!

If the patient tested positive for NTRK gene fusion, provide the gene for which he/she tested positive. In addition, it is asked if there was prescreening with IHC. After a positive IHC test, confirmation of NTRK gene fusion is needed by PCR, NGS or FISH.

Also give the date of the PCR, NGS or FISH test when NTRK gene fusion was confirmed. This date cannot be after the start of the NTRK-inhibitor treatment.

2.5. Comorbidities

Name variable	Type	Answer options
Comorbidity- Charlson Modified Index (not the current indication):	SS	No
		Yes*
*Type of comorbidity (**Charlson Modified index**):	MS + text	Myocardial infarction
		Peripheral vascular disease
		Cerebrovascular disease
		Congestive heart failure
		Connective tissue disease
		Mild liver disease
		Moderate-severe liver disease
		Moderate-severe renal disease
		Chronic pulmonary disease
		Peptic ulcer
		Hemiplegia
		Dementia
		Diabetes without damage to end-organs
		Diabetes with damage to end-organs
		Any tumour (without metastasis); please specify …
		Leukaemia (acute or chronic)
		Lymphoma
		Metastatic solid tumour; please specify …
		AIDS (not just HIV)

'Comorbidity' is described as the presence of one or more additional medical conditions, co-occurring with the primary condition (here: the NTRK-inhibitor indication) but not caused by it. The comorbidities should already be present prior to the start of the NTRK-inhibitor treatment. These comorbidities are important to register because they may affect patient outcome. The comorbidities do not include the current NTRK-inhibitor indication!

The **Charlson Comorbidity Index** (CCI) is used to collect the comorbidity information. It is among the best-known and widely used indices of comorbidity and consists out of 19 conditions. A single comorbidity score for a patient can be calculated based on the indicated comorbidities. The index is based on the International Classification of Diseases (ICD) diagnosis codes found in administrative data. For your information, a non-exhaustive list of ICD-10 codes for each comorbidity is provided in Appendix A.

Please indicate which of the specified conditions could have an influence at the start of NTRK-inhibitor treatment. The timeframe in which the comorbidity was or should be present, is dependent on the type of comorbidity:

- Most items relate to the past medical history of the patient (e.g. myocardial infarction, peptic ulcer, ...) and should not necessarily be active at the start of NTRK-inhibitor treatment
- For some items related to specific organ functions (e.g. renal disease, liver disease) the situation at the start of NTRK-inhibitor treatment should be considered. For example: acute kidney failure in the past medical history with a complete normal kidney function at the start of NTRK-inhibitor treatment is not an increased risk factor and should not be registered. The same is true for gestational diabetes.
- Only indicate a tumour or malignancy when it is diagnosed or treated within 5 years of the start of NTRK-inhibitor treatment. In this case, please also specify the type of malignancy.

2.6. Disease information at start NTRK-inhibitor treatment

2.6.1. WHO score

Name variable	Type	Answer options
WHO score at start NTRK-inhibitor treatment:	SS	0- Asymptomatic, normal activity
		1- Symptomatic, but ambulant
		2- Symptomatic, bedbound <50% of the day
		3- Symptomatic, bedbound >50% of the day
		4- Completely dependent, 100% bedbound
		Unknown

The **WHO performance score** is a classification system which evaluates the general welfare and daily activity of the patient. The answer options normally run from 0 to 5, where a score of 0 indicates a healthy person, while a score of 5 equals death. In this registration form, the answer options are limited from 0 to 4.

In contrast with the general cancer registration for a new diagnosis (MOC/COM, bijlage/annexe 55), this WHO status is the one at the start of NTRK-inhibitor treatment.

Score 0	Asymptomatic, normal activity	Fully active, able to carry out all activities, such as before the disease
Score 1	Symptomatic, but ambulant	Limited in heavy physical activity but ambulatory and able to perform light or sedentary work (e.g. small house chores, office job)
Score 2	Symptomatic, bedbound <50% of the day	Ambulatory and able to take care of themselves, but impossible to perform work activities. 'Active' more than 50% of the day
Score 3	Symptomatic, bedbound >50% of the day but not 100% bedbound	Only able to carry out a limited number of self-sufficiency tasks. Confined to bed or chair for 50% or more of the waking hours
Score 4	Completely dependent (on caretakers): 100% bedbound	Totally disabled. Can no longer take care of themselves. Totally confined to chair or bed

Note: When the WHO performance score is not specified but a Lansky or Karnofsky score is available, please use the following conversion table to determine the WHO performance score:

WHO score	Lansky/ Karnofsky score	Lansky level of performance (< 16 years)	Karnofsky level of performance (≥ 16 years)
0	100	Fully active; normal	Normal, no complaints or signs of disease
1	90	Minor restrictions in physically strenuous activities	Able to carry on normal activities; minor signs or symptoms of disease
	80	Active, but tires more quickly	Normal activity with effort
2	70	Restriction in and less time spent in active play	Care for self; unable to carry on normal activity or to do active work
	60	Up and around; minimal active play; keeps busy with quieter activities	Requires occasional assistance, but able to care for most of his needs
3	50	Gets dressed but lies around much of the day; no active play; able to participate in all quiet play and activities	Requires considerable assistance and frequent medical care
	40	Mostly in bed; participates in quiet activities	Disabled; requires special care and assistance
4	30	In bed; needs assistance even with quiet play	Severely disabled; hospitalisation indicated though death non-imminent
	20	In bed, often sleeping; play limited to very passive activities	Very sick; hospitalisation necessary; active supportive treatment necessary
	10	Does not get out of bed; does not play	Moribund

2.6.2. Disease status at start NTRK-inhibitor treatment

Name variable	Type	Answer options
Disease status at start NTRK-inhibitor treatment	SS	Locally advanced
		Metastatic *
* Date of diagnosis first metastasis	Date	(dd/mm/yyyy)
* Number of metastatic lesions at start NTRK-inhibitor treatment	NUM	…
* Localization of currently active metastatic lesions	MS	Adrenal metastases
		Bone (non-spinal) metastases
		Brain metastases
		Hepatic metastases
		Lung metastases
		Lymph node metastases
		(Para-) spinal metastases
		Other (oligo)metastatic lesion(s); please specify

The **variable disease status at start NTRK-inhibitor treatment** indicates if the current indication is locally advanced or metastatic. In case of metastasis, you also need to provide the date of the diagnosis of the first metastasis. The start date of NTRK-inhibitor treatment cannot be earlier than the date of diagnosis of the metastasis.

This is the date of (with decreasing priority):

1. First microscopic confirmation of the metastasis (cytological or histological)
2. First hospitalisation for the metastasis
3. First consultation for the metastasis
4. First clinical or technical diagnosis
5. Start of treatment for the metastasis

The **number of currently active metastatic lesion(s)** specifies the total number of metastatic lesion(s) present. Note that residual non-progressive metastases are NOT counted for the total number of currently active metastases.
In addition, also specify the **localisation** of the current active metastatic lesion(s). If the option 'other metastatic lesion(s)' is chosen, this should be further specified.

2.7. Previous treatments (before start NTRK-inhibitor)

Name variable	Type	Answer options
How many types of treatment did the patient receive before the start of NTRK-inhibitor for the current indication for which information is available?	NUM	(1-10)
Treatment type:	SS + Text	1. Chemotherapy
		2. Hormonal therapy
		3. Immunotherapy
		4. Targeted therapy
		5. Surgery *
		6. Radical radiotherapy *
		7. Radiofrequency ablation (RFA) *
		8. Other. Specify: …
Specify the treatment type:	Text	
Start date:	Date	(dd/mm/yyyy)
End date:	Date	(dd/mm/yyyy)
* Localisation:	Text	

Please specify how many types of treatment the patient received before the start of NTRK-inhibitor for the current indication for which information is available.

Note: If the patient received previous treatment(s) in another hospital, it is still the responsibility of the registering hospital to complete this information in this registration form.

Specify for each treatment in the table in chronologically order:

- The treatment type:
  - If the option 'other' was chosen, this should be further specified in the text field.
  - If a treatment line consists of different treatment types (e.g. chemo-immuno), each type should be entered as a separate type.
  - When a certain treatment type is re-started later in time, they should be entered as 2 separate types.
- Specify treatment type: give more information about the treatment type:
  - Chemotherapy: please specify
    - Generic name chemotherapeutic agent
    - Type of administration
    - Number of administrations and/or the cumulative dose and unit
  - Hormonal therapy (including corticosteroids): please specify
    - Type of hormonal therapy
    - Cumulative dose and unit
  - Immunotherapy (including monoclonal antibodies): please specify
    - Type of immunotherapy / monoclonal antibodies
    - For monoclonal antibodies: cumulative dose and unit
  - Targeted therapy: please specify
    - Type of targeted therapy
    - Cumulative dose and unit

- Surgery: please specify
  - Type of surgery: open, minimally invasive (+type), conversion please provide the type of surgery (open, minimally invasive)
  - Type of lymphadenectomy (if applicable)
  - Cumulative dose and unit
- Radical radiotherapy: Please specify
  - Radiation source:
    - Photon therapy: X-rays, cobalt, unknown/not mentioned
    - Hadron therapy: protons, carbon ions, …
    - Electron therapy
    - Radioisotope
    - Other: please specify
    - Unknown/not mentioned
  - Type of radiotherapy
    - External beam radiotherapy
      - 2D
      - 3D conformal radiation therapy (3D-CRT)
      - Intensity Modulated Radiation Therapy (Static beam IMRT, rotational beam IMRT (tomotherapy, RapidArc, VMAT))
      - Stereotactic radiosurgery (Gamma Knife / Cyberknife)
      - Intraoperative Radiation Therapy (IORT)
      - Other: please specify
      - Unknown/not mentioned
    - Internal radiotherapy/brachytherapy
    - Radioimmunotherapy
    - Other: please specify
    - Unknown/not mentioned
  - Cumulative dose (Gy)
  - Number of fractions
  - Boost? + Boost dose
- RFA: please specify
  - Type of RFA catheter used
  - Associated protocol used
- Other: please provide as much information as possible

- Start date and end date: the start and end date of that specific treatment.
  - If an exact date is not known, please enter 15/mm/yyyy (only month and year known) or 1/07/yyyy (only year known).
  - In case of a 1-day treatment, please enter this date also as end date.

Please also specify the localisation of the surgery, radical radiotherapy or RFA treatment.

2.8. General comments field

A general 'comments' field is provided in the WBCR application. All relevant, additional information may be added to the registration in this field.

This 'comments' field can be found at the bottom of the online registration form. Please fill out this field in English as much as possible.

3. Follow-up registration form end of treatment

The follow-up registration form end of treatment must be filled out 6 months after the end of the NTRK-inhibitor treatment. This form contains information until 6 months after the end of the NTRK-inhibitor treatment.

3.1. Administrative patient and treatment data

Please provide the same information for the patient and treatment as on the primary registration form.

3.2. NTRK-inhibitor treatment

3.2.1. Start and end date NTRK-inhibitor treatment

Name variable	Type	Answer options
Start date NTRK-inhibitor treatment:	Date	(dd/mm/yyyy)
End date NTRK-inhibitor treatment:	Date	(dd/mm/yyyy)
Reason for discontinuation	SS	Disease progression
		Death
		Adverse events
		Patient decision
		Other, please specify …

For the NTRK-inhibitor treatment, please provide the start and end date of NTRK-inhibitor treatment. Also, give the reason for discontinuation of NTRK-inhibitor treatment. If the option 'other' is chosen, this should be further specified.
If the treatment is still ongoing at the time of the follow-up registration, the date of the follow-up registration has to be filled out as the end date. In the comment field it must be specified that the treatment is still ongoing.

3.2.2. Treatment specifications

Name variable	Type	Answer options
Treatment formulation	SS	Capsule
		Oral solution
Starting dose	NUM	…. (mg)
Time daily	SS	Once daily
		Twice daily
Total number of days the patient received a reduced NTRK-inhibitor dose	NUM	…
Total number of days the patient did not receive NTRK-inhibitor	NUM	…

Specify if the patient is receiving NTRK-inhibitor as a capsule or as an oral solution. In addition, provide the starting dose in mg as well as the number of times per day this is taken.
If the patient received a reduced NTRK-inhibitor dose during the treatment period: give the number of days. If there were days during the treatment, the patient didn't receive any NTRK-inhibitor: specify the number of days as well.

3.2.3. Best overall response

Name variable	Type	Answer options
What was the best overall response to NTRK-inhibitor according to the RECIST or RANO criteria?	SS	Complete response
		Partial response
		Stable disease
		Progressive disease
		Could not be evaluated
Date of this best overall response	Date	(dd/mm/yyyy)

The **Response Evaluation Criteria in Solid Tumors (RECIST) criteria** standardise and simplify the response of patients during treatment. To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint (Eisenhauer EA, et al. Eur J Cancer 2009;45:228-47)

Tumour resonse	RECIST criteria
Complete response	Disappearance of all target lesions. Any pathological lymph nodes (whether target of non-target) must have reduction in short axis to <10mm.
Partial response	At least a 30% decrease in the sum of diameters of target lesions; taking as reference the baseline sum diameters.
Stable disease	Neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters
Progressive disease	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (note: the appearance of one or more new lesions is also considered progression).

The **Response Assessment in Neuro-Oncology (RANO) criteria** are used to assess response to treatment of high-grade gliomas. As with the RECIST criteria, the lesions must be measurable by either CT or MRI (Wen PY et al, J Clin Oncol 2010;28(11):1963-72).

Tumour resonse	RANO criteria
Complete response	Imaging features: disappearance of all enhancing disease (measurable and non-measurable); sustained for at least 4 weeks; stable or improved non-enhancing FLAIR/T2W lesions; no new lesions. Clinical features: no corticosteroids (physiological replacement doses allowed); clinically stable or improved.
Partial response	Imaging features: 50% of more decrease of all measurable enhancing lesions; sustained for at least 4 weeks; no progression of non-measurable disease; stable or improved non-enhancing FLAIR/T2W lesions; no new lesions. Clinical features: stable or reduced corticosteroids (compared to baseline); clinically stable or improved.
Stable disease	Imaging features: does not qualify for complete response, partial response, or progression; stable non-enhancing FLAIR/T2W lesions Clinical features: stable or reduced corticosteroids (compared to baseline); clinically stable.
Progressive disease	Imaging features: 25% or more increase in enhancing lesions despite stable or increasing steroid dose; increase (significant) in non-enhancing FLAIR/T2W lesions; not attributable to other non-tumor causes Clinical features: clinical deterioration (not attributable to other non-tumor causes and not due to steroid decrease)

Also include the date of this best overall response.

3.2.4. Adverse events

Name variable	Type	Answer options
Type of adverse event	MS	Fatigue
		Pyrexia
		↑ bodyweight
		Peripheral oedema
		Nausea
		Vomiting
		Constipation
		Diarrhea
		Abdominal pain
		Dizziness
		Headache
		Cough
		Dyspnoea
		Nasal congestion
		Arthralgia
		Myalgia
		Muscular weakness
		Back Pain
		Pain in extremity
		↓ Appetite
		Hypertension
		↑ ALT
		↑ AST
		Anaemia
		Neutropenia
		Hypoalbuminemia
		↑ alkaline phosphatase
		Other

Select only **CTCAE grades 3 or 4 (severe) adverse events** seen during NTRK-inhibitor treatment. Also indicate if the specific adverse event was a reason to decrease the NTRK-inhibitor dose. If a specific adverse event was a reason to stop the NTRK-inhibitor, this should also be indicated.

The Common Terminology Criteria for Adverse Events (CTCAE) is a descriptive terminology which can be utilized for Adverse Event (AE) reporting:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities on daily living (preparing meals, shopping for groceries or clothes, using the telephone, managing money, …)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities on daily living (bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden)
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to adverse event

3.3. NTRK-inhibitor treatment

Name variable	Type	Answer options
Were other treatments initiated after the start of NTRK-inhibitor and within 6 months after the end of NTRK-inhibitor treatment	SS	Yes*
		No
* Treatment type:	MS	1. Chemotherapy
		2. Hormonal therapy
		3. Immunotherapy
		4. Targeted therapy
		5. Surgery §
		6. Radical radiotherapy §
		7. Radiofrequency ablation (RFA) §
		8. Other
* Specify the treatment type:	Text	
* Start date:	Date	(dd/mm/yyyy)
* End date (if applicable)	Date	(dd/mm/yyyy)
§ Localisation:	Text	

Please specify if the patient received other treatments within 6 months after the end of NTRK-inhibitor treatment. If yes, specify for each treatment in the table in chronologically order:

- The treatment type:
  - If a treatment line consists of different treatment types (e.g. chemo-immuno), each type should be entered as a separate type.
  - When a certain treatment type is re-started later in time, they should be entered as 2 separate types.
- Specify treatment type: give more information about the treatment type:
  - Chemotherapy: please specify
    - Generic name chemotherapeutic agent
    - Type of administration
    - Number of administrations and/or the cumulative dose and unit
  - Hormonal therapy (including corticosteroids): please specify
    - Type of hormonal therapy
    - Cumulative dose and unit

- Immunotherapy (including monoclonal antibodies): please specify
  - Type of immunotherapy / monoclonal antibodies
  - For monoclonal antibodies: cumulative dose and unit
- Targeted therapy: please specify
  - Type of targeted therapy
  - Cumulative dose and unit
- Surgery: please specify
  - Type of surgery: open, minimally invasive (+type), conversion please provide the type of surgery (open, minimally invasive)
  - Type of lymphadenectomy (if applicable)
  - Cumulative dose and unit
- Radical radiotherapy: Please specify
  - Radiation source:
    - Photon therapy: X-rays, cobalt, unknown/not mentioned
    - Hadron therapy: protons, carbon ions, …
    - Electron therapy
    - Radioisotope
    - Other: please specify
    - Unknown/not mentioned
  - Type of radiotherapy
    - External beam radiotherapy
      - 2D
      - 3D conformal radiation therapy (3D-CRT)
      - Intensity Modulated Radiation Therapy (Static beam IMRT, rotational beam IMRT (tomotherapy, RapidArc, VMAT))
      - Stereotactic radiosurgery (Gamma Knife / Cyberknife)
      - Intraoperative Radiation Therapy (IORT)
      - Other: please specify
      - Unknown/not mentioned
    - Internal radiotherapy/brachytherapy
    - Radioimmunotherapy
    - Other: please specify
    - Unknown/not mentioned
  - Cumulative dose (Gy)
  - Number of fractions
  - Boost? + Boost dose
- RFA: please specify
  - Type of RFA catheter used
  - Associated protocol used
- Other: please provide as much information as possible

- Start date and end date: the start and end date of that specific treatment.
  - If a treatment line consists of different treatment types (e.g. chemo-immuno), each type should be entered as a separate type.
  - When a certain treatment type is re-started later in time, they should be entered as 2 separate types.
  - If an exact date is not known, please enter 15/mm/yyyy (only month and year known) or 1/07/yyyy (only year known).
  - In case of a 1-day treatment, please enter this date also as end date.
  - If a treatment is currently still ongoing, please enter 01/01/2100 as end date.

Note: If the patient received further treatment(s) in another hospital, it is still the responsibility of the registering hospital to complete this information in this registration form.
Please also specify the localisation of the surgery, radical radiotherapy or RFA treatment.

3.4. Survival status

Name variable	Type	Answer options
If the patient died, what was the cause of death?	SS	Related to the cancer(treatment); please specify: …
		Not related to the cancer(treatment); please specify: …
		Uncertain, relation to the cancer(treatment) cannot be excluded; please specify: …
		Unknown / not mentioned in the medical report

If the patient died, indicate the cause of death. For each option, please give more information.

3.5. General comments field

A general 'comments' field is provided in the WBCR application. All relevant, additional information may be added to the registration in this field.

This 'comments' field can be found at the bottom of the online registration form. Please fill out this field in English as much as possible.

4. Follow-up registration form 01/10/2023

This form should be filled out at the latest on 01/10/2023 (Larotrectinib) or 01/04/2024 (Entrectinib). All variables in this form are the same as these in 3. Follow-up registration form end of treatment.

Note: For those patients for whom the treatment is still ongoing on 15.09.2023 or 15.03.2024, the form "Follow-up registration End of treatment" also needs to be filled out 6 months after the end of the NTRK-inhibitor treatment.

5. Frequently asked questions (FAQ)

5.1. Registration in general

5.1.1. How can registrations be delivered to BCR?

One mode of registration is possible for this project, namely via the online WBCR application (see section 1.2 for all specifications). The WBCR manual can be consulted and downloaded from the BCR website (Dutch/French).

5.1.2. When should the registrations be delivered to BCR?

The start date of the 3-year convention is 1/04/2021 (Larotrectinib) or 1/10/2021 (Entrectinib); the end date is 1/04/2024 (Larotrectinib) or 1/10/2024 (Entrectinib). All patients within the convention target population should be registered if the date of e-health approval falls on or after 1/04/2021.

There are different registration time points:

- At the start of the treatment: the primary registration form must be completed at the latest 1 month after the eHealth application of the NTRK inhibitor treatment.
- At the end of the treatment: the follow-up registration form must be completed 6 months after the end of the NTRK inhibitor treatment
- For **larotrectinib**: on 01/10/2023: the follow-up registration form must be completed at the latest on 01/10/2023. This is only the case if treatment is still ongoing on 15/09/2023.
- For **entrectinib**: on 01/04/2024: the follow-up registration form must be completed at the latest on 01/04/2024. This is only the case if treatment is still ongoing on 15/03/2024.

See section 1.3 for all specifications

5.1.3. How should a patient without an INSZ/NISS number be registered?

Only in very rare cases, a patient will not have an INSZ/NISS number. In this case, please make sure to include all other requested administrative patient data, so that the patient can unambiguously be identified. If the patient is not domiciled in Belgium, please indicate the other country and the foreign zip code.

Also, the health insurance institution and number must be provided for the patient as well as the eHealth notification number. This is the number you received when applying for NTRK-inhibitor treatment approval via the eHealth platform.

5.1.4. How can I make corrections to send registrations?

Once a registration has been sent to BCR, it is impossible to modify the registered information in the BCR database yourself. The BCR should be contacted to make the necessary corrections in the database. **For WBCR users, please note that these corrections will not be visible when performing a WBCR download.**

The following options are possible:

- Preferred: Perform a new, complete and corrected registration, mentioning in the general comments field: "corrected version".
- Changes can be communicated via telephone to your Cancer Registry contact person (only if it concerns few errors). You will also be asked to confirm the changes via email, using ONLY the WBCR ID to identify the correct registration, **without other patient identification variables**:
- Via email to the project email address (NTRKinhibitor@kankerregister.org). **Very important: Patient identification information (such as name, INSZ/NISS, date of birth, …) cannot be communicated via email for privacy and confidentiality reasons!** Please only mention the WBCR reference/ID number (which is automatically assigned to each sent registration) to identify the registration in which corrections need to be carried out. If you download your registrations in an Excel file from WBCR, the WBCR reference/ID number can be found in column A.

In all cases, please clearly state for each registration which variable needs to be corrected, which incorrect information was first registered and to what this should be corrected.

5.1.5. Will I receive feedback on the patient registrations that were sent to BCR?

After each registration deadline, feedback will be sent about the completeness of the registrations. If data are missing, you can be asked to complete this information.

5.2. Inclusion criteria

5.2.1. What are the patient inclusion criteria?

The requirements for patient inclusion can be translated into the following concrete inclusion criteria for registration:

- patients with a Belgian health insurance
- have a neurotrophic receptor tyrosine kinase (NTRK) gene fusion without a known acquired resistance mutation
- tumour is locally advanced or metastatic, or surgical resection is likely to result in severe morbidity
- have no satisfactory alternative treatments
- after approvement at a multidisciplinary oncological consult (MOC)
- for whom NTRK-inhibitor treatment is requested and approved through the eHealth platform.

The **start date of reimbursement of Vitrakvi® (Larotrectinib) and Rozlytrek (Entrectinib)** is **1/04/2021 and 1/10/2021 respectively**. All patients for which the **date of the eHealth approval**, falls on or after 01/04/2021 are included in the target population and must be registered.

Patients who are already treated with Larotrectinib or Entrectinib before respectively 01/04/2021 and 01/10/2021 as part of a Compassionate Use Program and who met the conditions stated above before the start of the treatment, also have to be registered.

5.2.2. Should patients not domiciled in Belgium or without a Belgian health insurance be registered?

The convention clearly states that only patients with a Belgian health insurance are eligible for reimbursement of NTRK-inhibitor. The country of residence or the availability of a National number for social security (INSZ/NISS) does not matter.

5.3. Registration form variables

5.3.1. What if not enough information is available to fill out the requested variables?

It could be that the required information cannot be found in the available patient files. Please consult the responsible physician/pathologist to be able to fill out all requested variables.

Tip: Ask the physicians and pathologists to standardly include this information in the medical dossier of the patients.

5.3.2. In which language should the registrations be performed?

Please fill out all text variables in English as much as possible.

Appendix A: ICD-10 codes

A suggestion of related ICD-10 codes to the possible comorbidities, as discussed in section "2.3.4. Comorbidity- Charlson Modified Index" of this manual (based on Quan et al., Medical Care, 2005). Please note that this list is not exhaustive.

Comorbidity	ICD-10
Myocardial infarction	I21.x, I22.x, I25.2
Peripheral vascular disease	I70.x, I71.x, I73.1, I73.8, I73.9 I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Cerebrovascular disease	G45.x, G46.x, H34.0, I60.x - I69.x
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5 - I42.9, I43.x, I50.x, P29.0
Connective tissue disease	M05.x, M06.x, M31.5, M32.x - M34.x, M35.1, M35.3, M36.0
Mild liver disease	B18.x, K70.0 - K70.3, K70.9, K71.3 - K71.5, K71.7, K73.x, K74.x, K76.0, K76.2 - K76.4, K76.8, K76.9, Z94.4
Moderate-severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Moderate-severe renal disease	I12.0, I13.1, N03.2 - N03.7, N05.2 - N05.7, N18.x, N19.x, N25.0, Z49.0 - Z49.2, Z94.0, Z99.2
Chronic pulmonary disease	I27.8, I27.9, J40.x - J47.x, J60.x - J67.x, J68.4, J70.1, J70.3
Peptic ulcer	K25.x - K28.x
Hemiplegia	G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0 - G83.4, G83.9
Dementia	F00.x - F03.x, F05.1, G30.x, G31.1
Diabetes without any damage to end-organs	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Diabetes with damage to end-organs	E10.2 - E10.5, E10.7, E11.2 - E11.5, E11.7, E12.2 - E12.5, E12.7, E13.2 - E13.5, E13.7, E14.2 - E14.5, E14.7
Any tumour (without metastasis)	C00.x - C26.x, C30.x - C34.x, C37.x - C41.x, C43.x, C45.x - C58.x, C60.x - C76.x, C81.x - C85.x, C88.x, C90.x - C97.x
Leukaemia (acute or chronic)	
Lymphoma	
Metastatic solid tumour	C77.x - C80.x
AIDS (not just HIV positive)	B20.x **(only codes related to AIDS, not HIV+)**