NICE National Institute for Health and Care Excellence

Slides for public – all ACIC redacted

Please note some AIC information may now be publicly available upon publication of the EPAR

Larotrectinib for treating NTRK-fusion positive solid tumours [ID1299]

Lead team presentation

Lead team: Guy Makin, David Meads, Malcolm Oswald

ERG: York – CHE/CRD

Technical team: Gary McVeigh, Adam Brooke,

Christian Griffiths, Linda Landells

Company: Bayer

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Disease background

- The committee have been pre-briefed on the disease background

- Please find public briefing on:
  - Disease background
  - Description of the technology
  - The decision problem
  - Overview of the key clinical evidence

- Committee will begin discussion from slide 7

[redacted]

Disease background

- There are 3 NTRK gene fusions, NTRK1/2/3
- NTRK gene fusions are oncogenic drivers and are found in a wide variety of cancers including non-small cell lung cancer, breast cancer, pancreatic cancer and rare tumour types such as sarcoma and papillary thyroid cancer
- The company reports an overall prevalence of less than 1% but prevalence of NTRK gene fusion varies across different tumour types, ranging from less than 1% prevalence (for example in non-small cell lung cancer [NSCLC]) to >91% prevalence (for example in secretory carcinoma of the salivary gland and infantile fibrosarcoma)

- There is no established treatment pathway specifically for patients with *NTRK* fusion-positive tumours. Treatment is guided by tumour-specific care guidelines
- Treatment for rare, advanced cancers is often limited to surgery, radiotherapy and standard chemotherapy (with associated toxicity)
- More common tumour sites have guideline recommendations for multiple lines of therapy such as chemotherapy, targeted therapy and immunotherapy

[redacted]

Description of the technology

Technology being appraised	Larotrectinib (Vitrakvi, Bayer)
Mechanism	Selective TRK inhibitor of the TRKA, TRKB and TRKC genes, encoded by the NTRK1-3 genes
Indication	as monotherapy for the treatment of adult and paediatric patients with solid tumours that display a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion, - who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and - who have no satisfactory treatment options
Administration and dosage	Oral administration Adults: 100mg, twice daily until disease progression or unacceptable toxicity Paediatric population: based on body surface area. 100mg/m^2 twice daily with a maximum dose of 100mg until disease progression or unacceptable toxicity

[redacted]

Decision problem

	NICE Scope	Rationale for change
Population	People with NTRK fusion-positive advanced solid tumours who: • have either progressed on or not responded to prior therapies • are unfit for chemotherapy or for whom no curative therapy exists	• a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and • no satisfactory treatment options (to align with MA)
Intervention	Larotrectinib	-
Comparator	Established clinical management without larotrectinib	Weighted comparator (see model structure section)
Outcomes	overall survival • progression-free survival • response rate • duration of response • adverse effects of treatment • health-related quality of life.	-

[redacted]

Overview of the clinical evidence

- Evidence from 3 trials are combined into an efficacy evaluable dataset (n=102)
  - NAVIGATE, an ongoing basket trial for patients aged 12 an older with NTRK gene fusion who had received prior therapy or, in the opinion of the investigator, would be unlikely to derive clinically meaningful benefit from standard of care therapy. Contributes 62 patients to the pooled analysis.
  - SCOUT, an ongoing trial on paediatric patients with locally advanced or metastatic solid tumour or primary CNS tumour. Contributes 32 patients to the pooled analysis
  - LOXO-TRK-14001 a dose-finding study in patients with solid tumours harbouring NTRK fusion which contributes 8 patients to the pooled analysis

- The efficacy evaluable dataset was split into two datasets
  - ePAS2 – 93 efficacy evaluable patients with 14 tumour sites, response measured by RECIST 1.1 criteria
  - SAS3 – 9 patients with primary CNS tumours, response measured by RANO criteria

[redacted]

Patient perspectives

Submission from Sarcoma UK

- Sarcoma → rare cancer, affects all ages (paediatric to the elderly) but mainly younger people who are engaged in work and family life
- People with sarcoma fear recurrence, prognosis and limited available treatment options
- TRK inhibitors:
  - may reduce soft tissue sarcoma size allowing for surgical removal/resection of the previously untreatable tumour
  - High uptake is likely in the eligible population
- NHS England planning whole genome sequencing as standard for sarcoma

Submission from Roy Castle Lung Cancer Foundation

- One year survival for lung cancer is 37% → poor outlook
- There is a need to identify new targets and therapies for people with non-small cell lung cancer
- Objective response rate to TRK inhibitors is positive and good intracranial response for brain metastasis

[redacted]

Patient perspectives (continued)

Submission from GIST Support UK

- Surgery is a treatment option for GIST cancers diagnosed early but can be drastic
- Not all GIST cancers are the same → many do not respond to surgery and other current treatments
- Possible side effects of current treatments are extensive but usually can be managed
- NTRK gene fusions are the root cause of some GIST cancers
- under current protocols, NTRK gene fusion testing carried out when the patient has tested negative for all of the other known GIST mutations ("quadruple negative GIST")
- Addenbrookes Hospital in Cambridge are currently screening all people with quadruple negative GIST to find those with NTRK gene fusions
- Targeted therapies are what people with rare cancer are desperate to find and use to shrink and stop their tumours and "get their life back on track"

Clinician perspectives

Submissions from Royal College of Physicians (NCRI-ACP-RCP-RCR), two clinical experts

- Reduction in tumour size by more than 30% considered clinically significant
- True prevalence of NTRK fusion not clear because UK population has not been screened
- Treatment issues to resolve:
  - incorporating genomic profiling into pathways of care (especially where currently no molecular testing)
  - the optimal line of treatment for TRK inhibitors (which may vary by disease type)
- Screening options
  - nucleic acid based testing for all cancer patients (expensive)
  - nucleic acid based testing for rare cancers with high NTRK prevalence, else immunohistochemistry (IHC) test followed by a confirmatory DNA/RNA-based test if positive
- People with NTRK fusion would potentially gain significant benefit from a TRK inhibitor when standard-of-care treatments are exhausted and the only other option is best supportive care
- Education will be needed though oncology community is supportive of the concept of precision medicine and will adapt

[redacted]

Larotrectinib (Vitrakvi, Bayer)

Larotrectinib is indicated for the treatment of adult and paediatric patients that display a NTRK gene fusion who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory treatment option

- SPC: “The benefit of [larotrectinib] has been established in single arm trials encompassing a relatively small sample of patients… the effect may be quantitatively different depending on tumour type, as well as concomitant genetic alterations.”
- “For these reasons, [larotrectinib] should only be used if there are no treatment options for which clinical benefit has been established, or where such treatment options have been exhausted (i.e., no satisfactory treatment options)”
- Larotrectinib received a conditional marketing authorisation, committing to enrol 200 additional patients in NAVIGATE and SCOUT and submit a pooled analysis by June 2024.
- EPAR: “Among the anatomy-based tumour types studied in a clinical trial setting there are tumour types with single patients that did not achieve objective response and it is not known if tissue-specific bypass mechanisms such as was seen for BRAF inhibitors could exist also for NTRK fusions”

[redacted]

SPC – Summary of Product Characteristics
EPAR – European Public Assessment Report

Larotrectinib – consideration for CDF

The company are actively positioning larotrectinib for use within the CDF.

- Given the current level of uncertainty, the company propose that larotrectinib is made available within the CDF whilst data mature, and further data is collected.
- The company ask committee to consider how data collection within the CDF can reduce the inherent uncertainty of evaluating a histology independent indication.

How would data collection in the CDF align with the conditional marketing obligations?

[redacted]

Outstanding issues after technical engagement

- **Histology-independent specific issues**
  - Population and positioning (Issues 1, 2, 8 and 9)
  - Diagnosis (Issues 3 and 4)
  - Heterogeneity (Issues 5, 6 and 7)
  - Model structure and parameters (Issues 8, 9, 11, 12 and 16)
- **Appraisal specific issues**
  - Subsequent therapies (Issue 10)
  - Drug wastage (Issue 13)
  - Administration costs and resource use (Issue 14)
- **Decision issues**
  - Implementation and training costs (Issue 15)
  - End of life (Issue 17)
  - Innovation (Issue 18)
  - Cancer Drugs Fund (Issue 19)

[redacted]

Clinical evidence – efficacy evaluable patients

- Evidence from 14 tumour sites, 3 NTRK genes and 27 gene fusion partners

Tumour site	Pooled trial number (n=102)
Colorectal	[redacted]
Non-small cell lung	[redacted]
Breast	[redacted]
Sarcoma	[redacted]
Thyroid	[redacted]
Salivary gland	[redacted]
Pancreatic	[redacted]
Cholangiocarcinoma	[redacted]
Infantile fibrosarcoma	[redacted]
Melanoma	[redacted]
Bone sarcoma	[redacted]
Gastro-intestinal stromal tumours	[redacted]
Congenital mesoblastic nephroma	[redacted]
Appendix	[redacted]
Primary CNS	[redacted]

Gene fusion partner	Pooled trial number (n=102)
ETV6-NTRK3	[redacted]
TPM3-NTRK1	[redacted]
LMNA-NTRK1	[redacted]
24 other gene fusion partners	[redacted]

NTRK gene fusion status	Pooled trial number (n=102)
NTRK1	[redacted]
NTRK2	[redacted]
NTRK3 + (inferred NTRK3)	[redacted]

Low patient number by any given variable and rarity of the disease limits the ability to appraise by tumour site or gene fusion

[redacted]

Prevalence estimates by histology

Tumour site	NTRK prevalence	Cases of NTRK per year*
Colorectal	[redacted]	[redacted]
Non-small cell lung	[redacted]	[redacted]
Breast cancer	[redacted]	[redacted]
Sarcoma	[redacted]	[redacted]
Thyroid	[redacted]	[redacted]
Salivary gland (inc. MASC)	[redacted]	[redacted]
Pancreatic	[redacted]	[redacted]
Cholangiocarcinoma	[redacted]	[redacted]
Infantile fibrosarcoma	[redacted]	[redacted]
Melanoma	[redacted]	[redacted]
Bone sarcoma	[redacted]	[redacted]
Gastro-intestinal stromal tumours	[redacted]	[redacted]
Congenital nephroma	[redacted]	[redacted]
Appendix	[redacted]	[redacted]
Primary CNS	[redacted]	[redacted]

- Some rare **high NTRK prevalence** tumour sites are over-represented in trials, compared to the more common, low NTRK prevalence tumour sites
- ~30 tumour sites with identified NTRK gene fusions
- ~400 total solid tumour types (covered by MA)
- Highly uncertain NTRK gene fusion prevalence estimates
- Each tumour type will have a different definition of 'satisfactory' treatment options
- Estimated patient numbers require assumptions about eligibility that will depend on the treatment pathways

*patient number based on total NTRK fusion positive population, without consideration of eligibility

[redacted]

Treatment pathway – comparators

Tumour site	Comparator (company position)
Colorectal (+ Appendix)	BSC
Non-small cell lung	BSC
Breast	vinorelbine, gemcitabine, paclitaxel, doxorubicin and docetaxel
Sarcoma	BSC (paediatric patients – irinotecan and vincristine)
Thyroid	BSC
Salivary gland (MASC)	Cisplatin + vinorelbine
Pancreatic	5-FU + leucovorin
Cholangiocarcinoma	Gemcitabine + cisplatin
Primary CNS	Lomustine
Infantile fibrosarcoma	Irinotecan and vincristine
Melanoma (paediatric)	Mixed chemotherapy
Bone sarcoma	BSC
Gastro-intestinal stromal tumours	BSC
Congenital mesoblastic nephroma	Irinotecan and vincristine

- The company proposes it will be used 'last-line' after all satisfactory treatment options have been exhausted
- This positioning is used to model comparator treatments – largely best supportive care for more common cancers and chemotherapy for less common cancers
- Uncertainty whether this positioning is generalisable to the clinical evidence
  - [redacted] received prior surgery
  - [redacted] received prior systemic therapy ([redacted] at 1st or 2nd line, [redacted] 3rd or further)
- Uncertainty about positioning in clinical practice which would vary considerably by tumour site and rely on clinical judgement

[redacted]

Population and positioning

Issue	Resolved?
Prevalence of NTRK gene fusions **(Issue 1)**	Highly uncertain prevalence estimates – more data is needed to understand prevalence and characterisation of gene fusions, fusion partners and tumour histology.
Generalisability of NTRK gene fusion distribution in clinical evidence	Clinical evidence is unlikely to represent the distribution seen in clinical practice – this true distribution can only be estimated through further data collection
Tumour sites unrepresented in the clinical evidence	Tumour sites that are not represented in the evidence may respond to larotrectinib, this could be approximated – further data collection needed
Treatment pathway and positioning **(Issue 2)**	EPAR mandates that larotrectinib is used last line only, there is potential for pathway 'creep' as larotrectinib is used more widely – information about positioning/ commissioning criteria needed
Comparator treatments **(Issues 8 and 9)**	Comparator treatments are reliant on treatment pathway and positioning – to be discussed further in the *model structure* section

[redacted]

NTRK diagnosis – timeline

2019

- Current testing for NTRK gene fusions is available for MASC and secretory breast carcinoma. Paediatric cancers and sarcoma have funding for whole genomic sequencing (WGS). No other current tests could identify NTRK gene fusions

2020

- NHS England have committed to introducing next generation sequencing (NGS) for solid tumours at the point of diagnosis of locally advanced or metastatic disease for an estimated 100,000 patients a year. This could include the capability of identifying NTRK gene fusions through addition of targeted DNA/RNA gene panels. 2/7 Genomic Hubs ready for testing

2021

- All 7 Genomic Hubs around England will be ready for testing, genomic pathways become embedded in clinical practice and links made with clinical teams. It may take a further 12 months for molecular testing to become fully embedded in practice and further ramp up of uptake for genomic testing

[redacted]

Screening populations

Tumour site	Cancer incidence per year (England)	NTRK fusion incidence per year
Colorectal	[redacted]	[redacted]
Non-small cell lung	[redacted]	[redacted]
Breast (secretory*)	[redacted]	[redacted]
Sarcoma	[redacted]	[redacted]
Thyroid	[redacted]	[redacted]
Salivary gland (MASC*)	[redacted]	[redacted]
Pancreatic	[redacted]	[redacted]
Cholangiocarcinoma	[redacted]	[redacted]
Infantile fibrosarcoma	[redacted]	[redacted]
Melanoma	[redacted]	[redacted]
Gastro-intestinal stromal tumours	[redacted]	[redacted]
Appendix	[redacted]	[redacted]
Primary CNS (glioma)	[redacted]	[redacted]
Total (including other tumour sites with NTRK)	[redacted]	[redacted]

- NHS England suggests screening based on diagnosis of Stage III/IV cancer (approximately 100k patients per year)

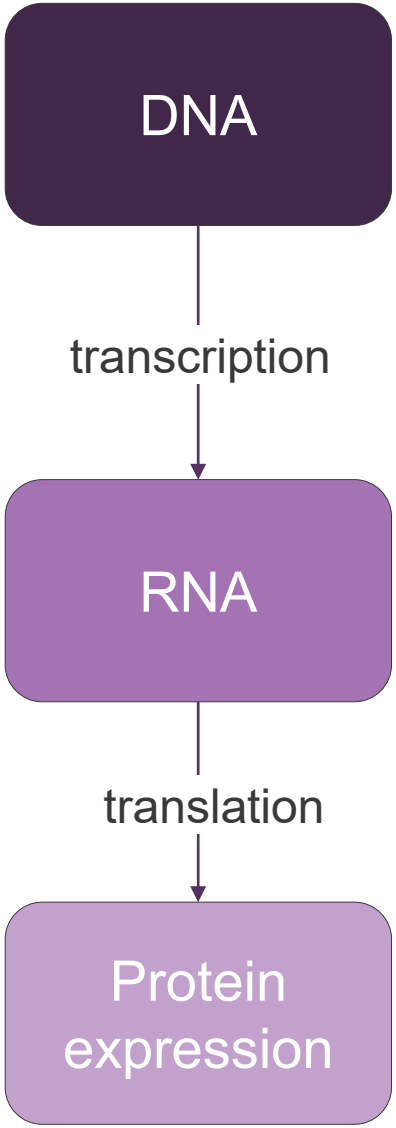
- ERG suggests individual screening pathways dependent on NTRK gene fusion rate and what testing is already available
- WGS is available for paediatric indications and sarcomas, for these tumour sites, WGS is assumed followed by confirmatory NGS screening
- For NSCLC, RNA-based NGS is already used, it is assumed the costs of adding a NTRK gene panel would be negligible
- All other patients receive IHC, followed by confirmatory NGS

- The company do not agree that NGS should be used for screening and consider that screening should happen at the point of no further satisfactory treatment options

[redacted] *secretory breast and MASC already test for NTRK gene fusion

patient number based on total NTRK fusion positive population, without consideration of eligibility

Genomic testing



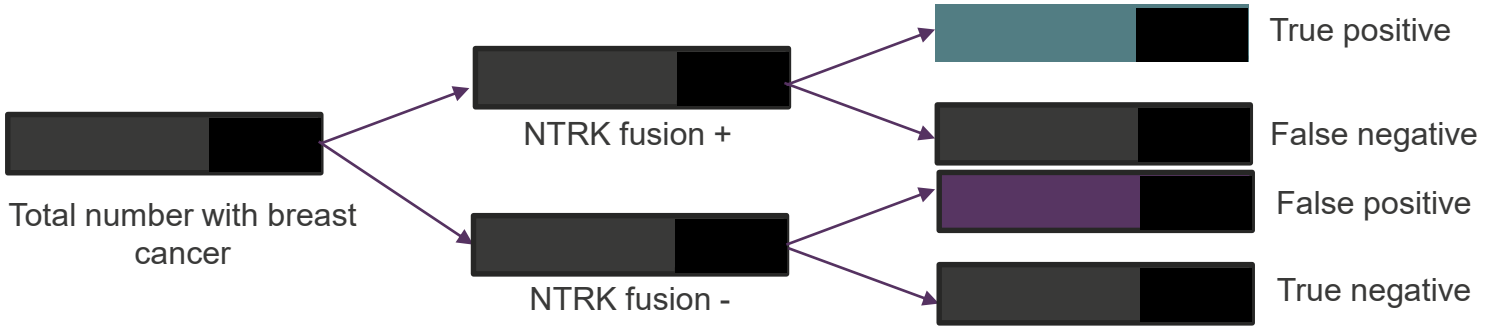
- NHS England suggest DNA/RNA-based NGS:
  - ❖ DNA can reliably find targeted panels with >70% sensitivity and very high specificity and can be added to existing gene panels at minimal cost
  - ❖ However DNA cannot easily find new fusion partners and may have difficult identifying NTRK2/3 gene fusions
  - ❖ RNA does not have these obstacles, has high sensitivity and specificity but is easily affected by tissue sample quality

- The ERG suggest a hierarchical approach to testing:
  - ❖ Screening for protein expression with immunohistochemistry testing for the majority of tumour types with lower sensitivity and specificity, confirmation with NGS
  - ❖ WGS for some patients who already receive it in the NHS has unknown sensitivity and specificity.

Diagnostic accuracy – screening example

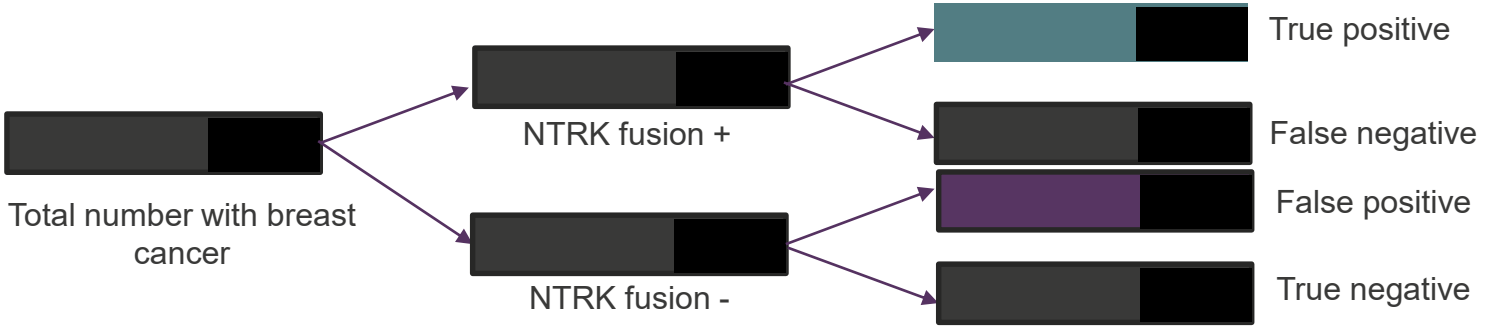
- For low NTRK prevalence tumour sites, diagnostic accuracy needs to be very high in order to avoid false positive results – for these patients, the tumour would not be expected to respond
- Below is a worked example using company breast cancer estimates of NTRK gene fusion prevalence estimate, literature values for sensitivity and 99% or 99.9% specificity

Prevalence	[redacted]
Sensitivity	81%
Specificity	**99%**



12% chance of positive identification being true

Prevalence	[redacted]
Sensitivity	81%
Specificity	**99.9%**



58% chance of positive identification being true

[redacted]

Diagnostic pathways - costs

"If a diagnostic test to establish the presence or absence of this biomarker is carried out solely to support the treatment decision for the specific technology, the associated costs of the diagnostic test should be incorporated into the assessments of clinical and cost effectiveness" – NICE methods guide

- **The company** consider that testing for NTRK gene fusions is part of the NHS Long Term Plan and that it will be offered as part of routine care. The NGS screening would not be used *solely* to support treatment choice for larotrectinib, so the company consider it inappropriate to model testing strategies or any costs associated with diagnostic testing.

- **The ERG** consider that until NHS England implements this diagnostic overhaul, screening pathways for each tumour site should be modelled and costed. ERG provides a scenario with these costs of the screening pathway included in the ICER.

- **NHS England** consider that all companies that benefit from this new service provision should provide a proportion of the costs.

[redacted]

Diagnosis

Issue	Resolved?
NTRK screening pathway **(Issue 3)**	DNA and RNA based screening for NTRK gene fusions will be available by 2021. There may be inequity of access to testing in the interim.
Screening costs **(Issue 3)**	The NICE methods guide was not designed to address a system wide overhaul in diagnostic techniques. Assessment of diagnostic costs requires an approximate number of eligible patients. What is the appropriate method of including testing costs?
Diagnostic accuracy **(Issue 4)**	For tumour sites with low NTRK prevalence, the diagnostic accuracy could lead to many false positive results for which patients will not respond to larotrectinib.

[redacted]

Heterogeneity – notes from the EPAR

- "*There are only few tumour types [those associated with ETV6-NTRK3] for which NTRK fusions have been **established as oncogenic 'drivers'** regardless of other characteristics. Larotrectinib has also shown important activity in GIST with NTRK after resistance/relapse with imatinib (ORR=5/5) and this likely reflects a similar role for NTRK fusions. For these conditions… **it is possible to conclude that efficacy has been established**."*
- "***For other conditions**, the role of NTRK fusions as oncogenic "drivers" is **not properly studied** and well-established. There are insufficient data to establish the activity of larotrectinib due to lack of comprehensive sequencing of tumour tissue prior to treatment, the small sample size in different tumour types, the **significant heterogeneity** observed in terms of ORR coupled with the notably very low ORR observed in different tumour types (ORR=0%-33%), especially in those common tumour types where occurrence of NTRK gene fusion is rare (lung, colon, breast)."*
- *"To further develop the product across other tumour types, or **to establish independence from tumour type**, it is important to collect convincing biological and clinical evidence to understand the resistance mechanisms involved, especially primary resistance, the role of concomitant biological and other characteristics that may explain the **observed heterogeneity or lack of activity**, and to confirm any reasonable extrapolations using reasonably powered studies to detect sufficient activity in different tumour types, in particular the more common cancers."*

[redacted]

Heterogeneity – company position

- The company model structure assumes homogeneity of response and survival outcomes (see model structure section)
- The company believe that "*consideration of response by tumour location only serves as a distraction and introduces the potential for decision-making to be based on chance findings*"
- The company refused to provide time-to-event survival data by tumour location because:
  - They consider that the data are too limited in patient numbers
  - Exploration of time-to-event outcomes in a Bayesian framework would be academic
  - They are discussing post-marketing commitments with the EMA that will provide a more substantial basis to assess tumour heterogeneity
- The statistical protocol of NAVIGATE 'basket' trial used Simon's two-stage design; planned if 1 in 7 patients respond to larotrectinib, within 7+ cohorts recruited by tumour type, this would show sufficient evidence to expand the cohort
- This was later amended for the efficacy evaluable analysis to pool all patients regardless of tumour type, despite not completing the formal assessment of response in the trial design (e.g. biliary/cholangiocarcinoma [redacted])
- EPAR states that type 1 error control is lost upon pooling and introduces the possibility of selection bias

[redacted]

Bayesian Hierarchical Model - response

Tumor Type	N	Responders
Overall	93	[redacted]
Soft tissue sarcoma	[redacted]	[redacted]
Salivary gland	[redacted]	[redacted]
Infantile fibrosarcoma	[redacted]	[redacted]
Thyroid	[redacted]	[redacted]
Lung	[redacted]	[redacted]
Melanoma	[redacted]	[redacted]
Colon	[redacted]	[redacted]
GIST	[redacted]	[redacted]
Bone sarcoma	[redacted]	[redacted]
Cholangiocarcinoma	[redacted]	[redacted]
Appendix	[redacted]	[redacted]
Breast	[redacted]	[redacted]
Congenital mesoblastic nephroma	[redacted]	[redacted]
Pancreas	[redacted]	[redacted]

- ERG suggests Bayesian Hierarchical modelling as an approach to quantify heterogeneity of response
- This framework takes response data for individual tumour sites, assumes some response data is exchangeable between them
- This prevents extreme results such as 0% or 100% response and gives less influence to tumour types with fewer individuals or events
- Methodology was developed specifically for the analysis of basket trials and is particularly useful where data are limited
- Similar approach to a random-effects meta-analysis
- It can be used to create an adjusted ORR based on the pooled tumour types with credibility intervals, using the assumption of a common effect between them

[redacted]

Bayesian hierarchical model

Bayesian hierarchical model - output

- The BHM model decreases the ORR from 72% from the company submission to [redacted] because it accounts for across-site heterogeneity
- The predicted distribution of an unevaluated tumour site is shown above which suggests a broad range of possible response rates in a new tumour site – this ORR and distribution can be used in economic modelling (see model structure)
- Inclusion of primary CNS tumours ([redacted]) into the BHM decreases the ORR to [redacted] although response for primary CNS tumours is measured using different response criteria. Larotrectinib may have a lower effective dose within the brain because of potential issues crossing the blood brain barrier
- ERG also provided two scenarios for the highest response in the model ([redacted]) and the lowest response in the model ([redacted]) to show the effect on the ICER

[redacted]

Bayesian Hierarchical Model - PFS

- Response is not explicitly used in the company base case - Bayesian Hierarchical Modelling can also be used for survival estimates, simulated results are shown below for PFS
- High uncertainty due to limited data available for time-to-event outcomes and immaturity of the data, although there is strong evidence of heterogeneity in time-to-event outcomes

[redacted]

Heterogeneity

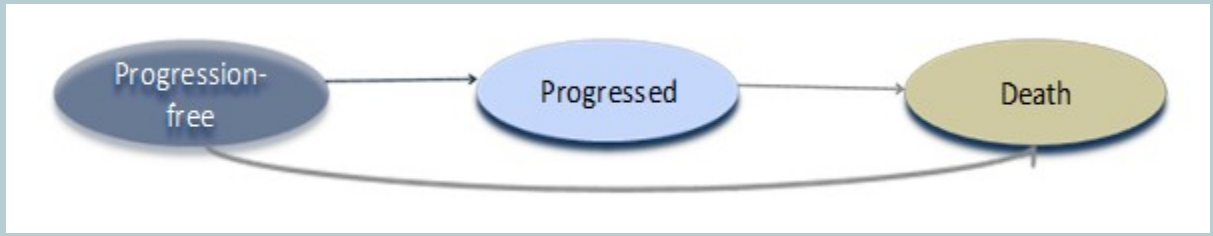
Issue	Resolved?
Heterogeneity of response by tumour type **(Issue 7)**	BHM provides a framework for assessing heterogeneity of response. This framework is used in the model structure and ICER estimation – additional response data is required for a wide range of tumour sites
Heterogeneity of survival outcomes PFS and OS by tumour type **(Issue 7)**	The company have not provided survival data, and it is likely to be too immature to be effective – further data maturation is required.
Statistical protocol of the 'basket' trial **(Issue 6)**	Response by tumour site has not been tested due to the pooling of the studies, cannot assume response for all tumour sites.
Inclusion of Primary CNS tumours in the ORR analysis **(Issue 5)**	This issue affects modelling choice and ICER estimation

[redacted]

Model structure – company overview

Company base case -

Historical comparator analysis: the company structure is based on a partitioned survival model with 3 mutually exclusive health states (progression-free, progressed and dead) commonly found in oncology models.



Because the evidence comes from single arm trials, the comparator arm was populated with naïve comparison to previous NICE appraisals of 'last-line' treatments for each tumour type. These values were extracted from NICE TAs where available and literature values where none were available.

Confirmatory model structures -

Response-based analysis: a dual partitioned survival model where PFS and OS from non-responders to larotrectinib populate the comparator arm.

Previous line of treatment analysis : Measures individual time to progression on previous treatment to populate PFS of the comparator arm, uninformative for OS

[redacted]

Historical comparator structure

Treatment arm:

- PFS and OS curves represent the single arm observed survival of entire efficacy evaluable population (n=102)
- There is no ability to adjust or compare the population based on any potential heterogeneity issue (most populations are too small to consider individually)
- Assumes homogeneous response to treatment and homogeneous natural history of every tumour type

Historical comparator structure

Comparator arm:

- PFS and OS curves here represent a combined estimate based on 12 individual ‘engines’ that use PFS and OS from selected ‘last-line’ treatments extracted from NICE TAs and literature values.
- Represents a naïve comparison with combined estimate of previous NICE decisions
- These are weighted by the tumour types observed in the efficacy evaluable population. Possible to adjust these comparator arms to alternative weightings but this will not reflect clinical evidence base

Historical comparator structure

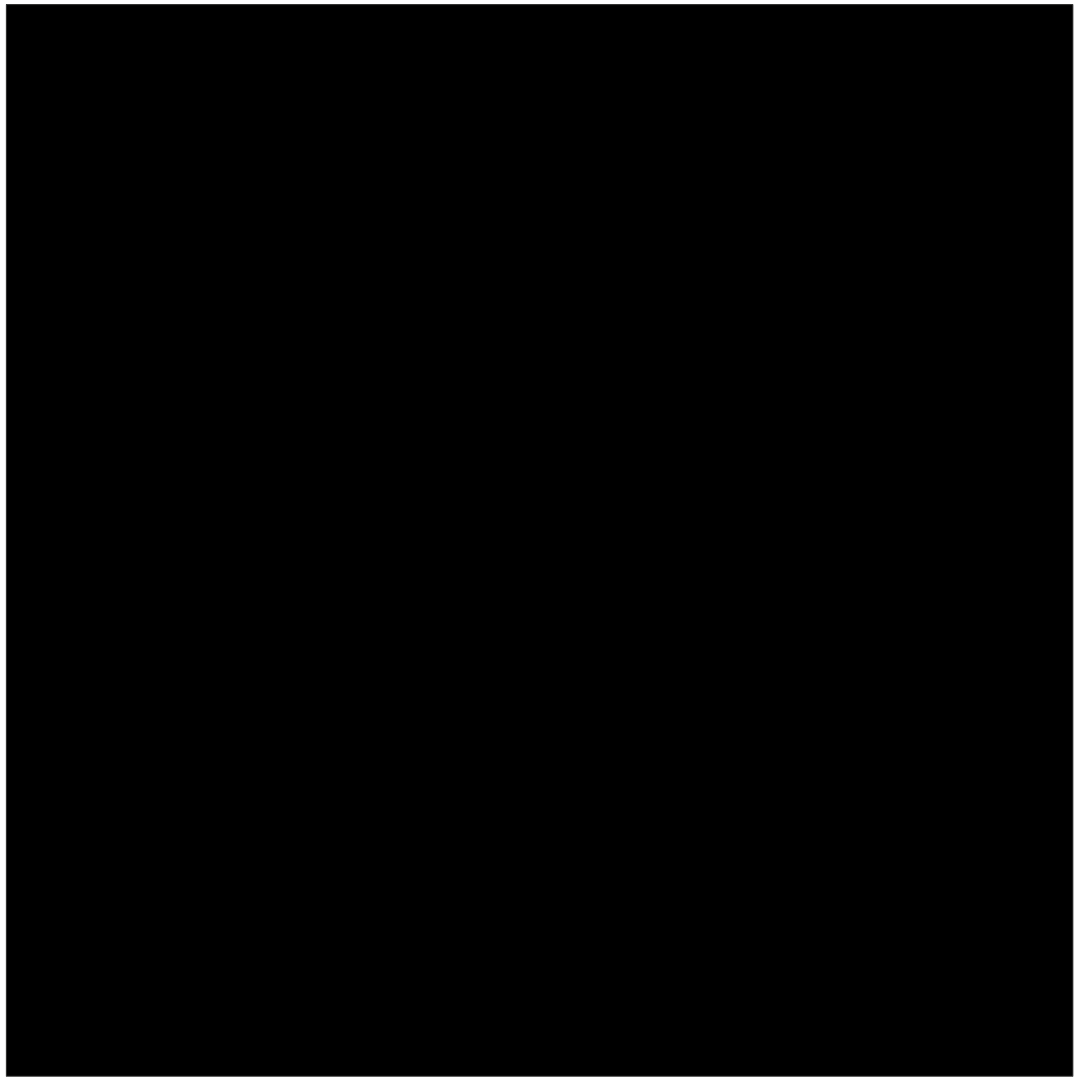
Confirmatory analyses - company

- The company performed a response-based analysis which involves stratifying the cohort by response status creating separate PFS and OS extrapolations based on this
- The non-responder arm is assumed to be the comparator (requires the assumption that no response is equivalent to BSC) and the treatment arm is a combined estimate of responders and non-responders
- ICER provides similar results to other analyses but the company did not consider it appropriate due to few non-responders and few events.
- ERG considered this analysis the most useful and further explored in their base case.

- The company performed a growth modulation index (GMI) comparison using time to progression on last line of therapy compared to current PFS for the same patient (for n=[redacted] patients)
- The ratio of this time (TTP_{t-1}/PFS) was used as a hazard ratio to the larotrectinib arm to approximate a comparator arm PFS – and the assumption that OS behaves equivalently
- ICER provides similar results to other analyses
- The ERG noted concerns with how this approach was implemented and also considered it to be unreliable as it is based on a patient's previous unsuccessful line of therapy which may not represent BSC – ERG did not consider this approach feasible because Bayer did not provide sufficient data and this approach is uninformative for OS

[redacted]

Response-based analysis – ERG preferred method



- ERG considered the response-based analysis most appropriate because it may provide a more transparent and potentially flexible alternative to modelling comparator effectiveness than the pooled historical comparator. It is less affected by confounding from subsequent lines of treatment and imbalance of patient characteristics
- Also allows for adjustment of response rates, the ERG used this analysis to input the ORR output from the BHM ([redacted] dependent on primary CNS inclusion in the model)
- However, there may be uncertainty from further reducing sample size ([redacted] total progressed) and ([redacted] total mortality)
- Requires assumption of a surrogate response between response rates and time-to-event outcomes
- ERG used response-based analysis in their base case

[redacted]

BHM – Bayesian Hierarchical Model

Utility values

- Utility values for larotrectinib arm were derived from HRQoL data collected in SCOUT (PedsQL data) and NAVIGATE (EQ-5D-5L data) mapped to EQ-5D-3L
- Utility values for the weighted comparator were collected as part of the construction of the comparator arm by collection of EQ-5D-3L utilities accepted in NICE TAs, weighted by distribution in the model and assumptions/ literature values where no TAs are published

	Larotrectinib		Weighted comparator	
	Pre-progression	Progressed	Pre-progression	Progressed
Company base case	[redacted]	[redacted]	[redacted]	[redacted]
ERG scenario	[redacted]	[redacted]	[redacted]	[redacted]

ERG comment:

- The analysis is informed by a small number of observations (progressed disease state is derived from [redacted] assessments in [redacted] patients – [redacted] of whom were children). Likely biases the utility values in favour of larotrectinib.
- Provided a scenario where post-progression utility is the same between treatment arms, plausible conservative assumption given the lack of data
- It is unclear why pre-progression utility would be different between treatment arms as most patients would be receiving BSC without chemotherapy, no scenario provided

[redacted]

Paediatric tumours – cure model

- The company suggest a cure model may be appropriate for some patients, particularly paediatric patients ([redacted] paediatric sarcoma, [redacted] infantile fibrosarcoma and [redacted] congenital mesoblastic nephroma patients in SCOUT).
- These patients were recruited because they had “no other curative options besides amputation or disfiguring surgery”.
- These patients may have survived without larotrectinib but received amputation or disfiguring surgery and the accompanying lifelong reduction in quality of life

- Comparator ‘engine’ for these tumour sites uses survival data for progressed or relapsed rhabdomyosarcoma where patients are not modelled to reach adulthood ([redacted] of model contribution)
- Model structure (time horizon of 80 years) is inappropriate for paediatric tumours for which there is a potential cure as this is not accounted for in the partitioned survival analysis

[redacted]

Model structure and parameters

Issue	Resolved?
Constructing a comparator arm/ comparator treatments **(Issues 8 and 9)**	Each model structure uses different assumptions about the comparator. Highly dependent on treatment pathway which requires further data collection
Model structure **(Issue 11)**	Each model structure has structural uncertainty, if the outputs concur then that could reduce uncertainty. Further data collection could inform model choice.
Extrapolation of OS and PFS **(Issue 12)**	Extrapolation does not provide meaningful results due to the immature data. In the absence of robust evidence, the most conservative assumptions should be assumed.
Utility values **(Issue 16)**	Pre- and post- progression survival utility values used likely bias in favour of larotrectinib.

Post-progression survival

- ERG considers the modelled post-progression survival for larotrectinib to be implausible

	Larotrectinib	Weighted comparator
Progression-free LYG	[redacted]	[redacted]
Progressed LYG	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]

- The progressed LYG is higher than both the progression-free LYG and the overall survival of the historical comparator treatment. The company did not propose a biologically plausible mechanism for this life extension.
- This could be an artefact of the highly uncertain extrapolation or related to the high proportion of patients that go on to receive further larotrectinib ([redacted]) or an experimental treatment (LOXO-195, [redacted] patients) for TRK-inhibitor resistant populations
- ICERs are highly sensitive to the overall survival extrapolation. Because of the difficulty of adjustment in this decision problem, the ERG provided two scenarios where the post-progression survival of larotrectinib is equal to progression-free survival of larotrectinib and the overall survival of the weighted comparator

[redacted]

Model assumptions

Issue	Resolved?
Drug wastage and dose adjustment **(Issue 13)**	ERG's adjustment to the base case dosing for paediatric patients is appropriate. Drug wastage should be incorporated but had minimal impact on the ICER.
Administration costs **(Issue 14)**	Inclusion of administration costs for oral chemotherapies is appropriate and has modest impact on the ICER.
Subsequent treatments and post-progression survival **(Issue 10)**	Scenarios have large impact on ICER but allow for biologically plausible consideration of impact of confounding from post-progression treatments and uncertain extrapolation.

Company base case

- Including company's PAS price gives the following deterministic ICER

	Larotrectinib	Comparators	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]	[redacted]
ICER	-	-	£35,309

[redacted]

ERG base case

- ERG adjustments to the base case included revising the paediatric dose of larotrectinib which likely underestimated the dose of larotrectinib in clinical practice
- ERG also used the response-based survival model with updated response rates from the BHM (two outputs dependent on inclusion of primary CNS response in the BHM)
- Conservative assumptions were used in the extrapolation of overall survival in the response-based model (Gompertz extrapolation)

64% ORR scenario	Larotrectinib	Comparators	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]	[redacted]
ICER	-	-	£48,872

57% ORR scenario	Larotrectinib	Comparators	Incremental
Total costs	[redacted]	[redacted]	[redacted]
Total LYG	[redacted]	[redacted]	[redacted]
Total QALY	[redacted]	[redacted]	[redacted]
ICER	-	-	£49,621

[redacted]

ERG exploratory analysis

Scenario	Total inc. costs	Total inc. QALYs	Total inc. LYG	ICER
Adjusted company base case	[redacted]	[redacted]	[redacted]	£35,957
1. ERG base case (57% ORR)	[redacted]	[redacted]	[redacted]	£49,621
2. Post-progression survival equal to comparator	[redacted]	[redacted]	[redacted]	£94,444
3. Post-progression survival equal to comparator OS	[redacted]	[redacted]	[redacted]	£71,318
4. Post-progression utility equal to comparator	[redacted]	[redacted]	[redacted]	£58,047
5. Tumour-specific response rate – IFS (highest response in BHM)	[redacted]	[redacted]	[redacted]	£47,208
6. Tumour-specific response rate – Colorectal (lowest response in BHM)	[redacted]	[redacted]	[redacted]	£51,762
7. Inclusion of NTRK testing cost	[redacted]	[redacted]	[redacted]	£55,491
Technical team base case – cumulative impact of scenarios 1, 2 and 4	[redacted]	[redacted]	[redacted]	£97,923

[redacted]

Innovation – (Issue 18)

Committee to consider if these treatments are **a step-change** in the treatment of cancer and if this innovation makes a significant and substantial impact on benefits, **unlikely to be included in the QALY calculation**

The company considers:

- Larotrectinib is a paradigm shift in the way cancer is treated, based on causation as opposed to tumour location
- A step towards delivering 'personalised medicine' in cancer patients

The **technical team** considers:

- The NTRK gene target is a newly identified rare gene fusion that occurs in a wide range of tumour types – larotrectinib shows response in many of these
- One of the first site-agnostic treatments to be appraised by NICE
- Major innovation already being led by NHS in developing more sophisticated strategies to improve genomic testing in clinical practice
- Appraisal of the first site-agnostic treatments represents potential for a future service redesign based on biological marker rather than histology

Committee to consider whether larotrectinib represents a step-change in treatment and if there are any substantial impact on benefits not captured in the QALY calculation

[redacted]

Implementation – (Issue 15)

Committee are asked to consider any likely constraints on the **resources required to support the implementation** of the appraised technologies and comment on the **impact this may have on the implementation timescale**

- Larotrectinib is for use within the CDF so routine commissioning implementation timescale does not apply
- Overhaul in diagnostic pathways likely to impact implementation – 2 of 7 regional Genomic Hubs ready to receive samples

- Additional training may be required:
  - Oncologists: new concepts associated with tumour-agnostic therapies → eligible tumour types, diagnostic pathway, position in treatment pathways, safety profile, collection of tissue sample
  - Pathologists: material handling

Committee to consider potential for phased uptake based on diagnosis and training requirements as part of implementation within the CDF

[redacted]

End of life – (Issue 17)

- For patients with **short life expectancy**, normally less than 24 months
- The treatment has the prospect of offering an **extension to life**, normally of a mean value of at least an additional 3 months compared with current NHS treatment
- The estimates of extension to life are sufficiently **robust** and can be shown or reasonably inferred from either PFS or OS

- NICE Methods guide

- End of life criteria not designed for histology independent treatments
- Likely that a proportion of indicated population meets EoL criteria and a proportion do not when stratifying by histology-based treatment population
- Clinical evidence available to inform committee decision:
  - Does not include distribution of patients that meets end-of-life
  - Does not include all tumour types included in the indication
  - Uncertainty around positioning in treatment pathway → impacts on estimate of overall survival
- The model structures do not allow for robust evidence for life extension criterion by tumour type, but life expectancy is independent of the model and is therefore a more useful criterion for discussion

[redacted]

End of life: life expectancy

Tumour site	Meets life expectancy?
Colorectal	Probable
Non-small cell lung	Probable
Breast (secretory)	Probable
Sarcoma	Life expectancy ~24 months
Thyroid	Life expectancy >36 months
Salivary gland (MASC)	Probable
Pancreatic	Probable
Cholangiocarcinoma	Probable
Primary CNS	Probable
Infantile fibrosarcoma (assumed same as paediatric sarcoma)	Life expectancy ~24 months
Melanoma (paediatric)	Probable
Bone sarcoma	Probable
Gastro-intestinal stromal tumours	Probable
Congenital mesoblastic nephroma (assumed same as paediatric sarcoma)	Life expectancy ~24 months

[redacted]

- Using estimate mean overall survival from the modelled comparator data shows that most tumour sites meet life expectancy criteria
- Thyroid cancer accounts for [redacted] of NTRK population estimate and [redacted] of the evidence base. All ‘amber’ tumour sites account for [redacted] of the NTRK population estimate and [redacted] of the evidence base
- If full end-of-life weighting is applied, patients with NTRK fusion positive thyroid cancer will receive a treatment based on end-of-life decision from a different population

Equalities

- Presence of a genetic marker is not a protected characteristic
- Cancer is a protected group through disability being a protected characteristic
- Prevalence of NTRK gene fusion is rarer in some tumour types compared with others – optimised decisions may indirectly discriminate against people with some cancer types
- This may pursue a **legitimate objective** (based on cost-effectiveness) but must be **proportionate** (least discriminatory action that will meet legitimate objective)
- Equalities position is unclear for underrepresented/unrepresented tumour sites

Histology-independent issues

- Plausible potential for cost-effectiveness for entry into the CDF (including end-of-life decision) may apply to some tumour sites and not to others.
- In a case where plausible potential for cost-effectiveness is considered met for the whole population with end-of-life threshold, people would be able to access therapy that would have otherwise be considered cost-ineffective based on conventional thresholds

Evidence issues

- Some tumour types included in the indication do not have any clinical effectiveness data or have data from very few patients

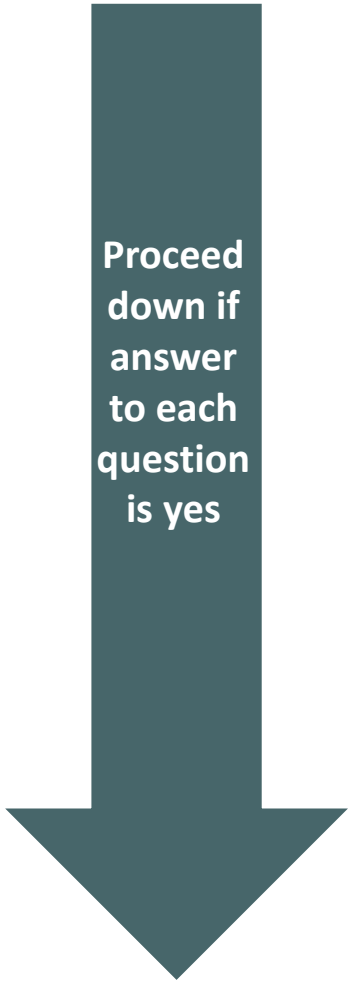
Diagnosis issues – equity of implementation

- Service provision has not yet been rolled out nationally

Committee to consider the clinical and/or scientific rationale for generalising the available evidence to all tumour sites including unrepresented sites

[redacted]

CDF recommendation criteria



Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF (invite company to submit CDF proposal)

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required , and number of patients in NHS in England needed to collect data.

[redacted]

○ Does larotrectinib meet the criteria for entry into the CDF?

CDF – Potential data sources

Data source	Summary. See draft DCA for further details
Ongoing clinical trials	• Further patient recruitment and more mature data • Annual reports planned for the pooled analysis in March each year • Final data-cuts: [redacted] (NAVIGATE) and [redacted](SCOUT)
Real-world evidence collected within CDF (CDF-RWE): Blueteq, SACT, Molecular dataset	Usefulness of real-world data is dependent on the type of CDF recommendation that is made and how testing is rolled out in clinical practice. Further details see 'Committee training slides October 22'
Non-interventional study (ON-TRK)	• International, investigator-led study • Final report non-pediatric: [redacted] pediatric: [redacted] • Overlap with RWE that could be collected within CDF - Notable exception is response rate by BICR • Further details available in protocol
EURACAN	• Company-led initiative. Currently in early exploratory stage • Annual reports planned • European registry for rare adult solid tumour cancers • Overlap with RWE that could be collected within CDF
Genomics England	• Company-led initiative. Currently in early exploratory stage • Aim to understand natural history of NTRK gene fusion

CDF – Potential data sources

Source(s) likely resolve area of clinical uncertainty	Source(s) may potentially resolve area of clinical uncertainty	Unlikely or unknown that the area of uncertainty could be resolved

Issue	Description	Potential primary source*
1	Prevalence + distribution of NTRK	CDF-RWE
2	Generalisability of the trial distribution to the population	CDF-RWE
3	Screening pathway, testing costs	CDF-RWE
4	Diagnostic accuracy	
7	Heterogeneity of response	Trial; CDF-RWE; ON-TRK
8+9	Robustness of control arm	Genomics England#
10	Subsequent therapies	CDF-RWE
12	Immaturity of the data	Trial
16	Post-progression utility state	Trial
17	EoL criteria	CDF-RWE; Genomics England#

* Multiple other sources may provide supportive evidence
# Company-led initiative in early exploratory stage. Unclear if this source may address uncertainty

[redacted]