NICE National Institute for Health and Care Excellence

Slides for public
all ACIC redacted

Entrectinib for treating NTRK fusion-positive solid tumours [ID1512]

Lead team presentation

Lead team: Guy Makin, Malcolm Oswald, Peter Hall

ERG: CRD & CHE - York

Technical team: Gary McVeigh, Emily Eaton Turner, Christian Griffiths, Linda Landells

Company: Roche

20th November 2019

Traffic light system

- Traffic light system has been introduced to indicate which issues require the most amount of discussion and to help prioritise committee's time

Issue	Resolved?
Green	The issue has been explored in the technical report and has a final technical team judgement, minimal impact on decision or no discussion required
Amber	The issue has an impact on uncertainty which may be resolved via further data collection or should be factored into the committee's judgement of uncertainty. Discussion may not help decision-making
Red	The issue has a large impact on the ICER and the committee needs to make a decision in order to understand impact on the assumptions in the appraisal, discussion required

Disease background

- The committee have been pre-briefed on the disease background
- Briefing available at the top of the technical report

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

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

Entrectinib (Rozlytre, Roche)

Anticipated marketing authorisation (MA):

“[redacted]

- [redacted]
- [redacted]”

* [redacted]

[redacted]”

[redacted]

Draft SmPC pre-CHMP (CHMP opinion expected [redacted])

- Section 4.4 – efficacy across tumour types:

  “[redacted]”

- “[redacted]”

NICE

SmPC – Summary of Product Characteristics
CHMP – Committee for Medicinal Products for Human Use

Entrectinib – consideration for CDF

The company are actively positioning entrectinib for use within the CDF

- Given the current level of uncertainty, the company propose that entrectinib 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

Outstanding issues after technical engagement

- **Histology-independent specific issues**
  - Population and positioning (Issues 2, 6, 7 and 11)
  - Diagnosis (Issues 3, 4, 5)
  - Heterogeneity (Issue 9)
  - Model structure (Issues 10 and 14)
- **Appraisal specific issues**
  - Prognostic factors (Issue 12)
  - Subsequent therapies (Issue 13)
  - Survival extrapolation (Issue 15)
  - Dose intensity (Issue 16)
  - Administration costs and resource use (Issue 17)
  - Utility values (Issue 19)
- **Decision issues**
  - Implementation and training costs (Issue 18)
  - Innovation (Issue 22)
  - End of life (Issue 21)
  - Cancer Drugs Fund (Issue 23)

Clinical evidence – efficacy evaluable patients

- Company's efficacy evaluable data set (n=54) included 13 tumour types (10 sites), 3 NTRK genes & 20 fusion partners
- Primary CNS and paediatric tumours added after technical engagement

Tumour site	ID1512 population (n=66)
Colorectal	[redacted]
Non-small cell lung	[redacted]
Breast	[redacted]
Sarcoma	[redacted]
Thyroid	[redacted]
Salivary gland (MASC)	[redacted]
Neuroendocrine	[redacted]
Pancreatic	[redacted]
Gynaecological	[redacted]
Cholangiocarcinoma	[redacted]
Primary CNS	[redacted]
Infantile fibrosarcoma	[redacted]
Melanoma	[redacted]

NTRK gene fusion status	Efficacy evaluable dataset (n=54) n (%)	Number of different fusion partners
NTRK1	22 (40.7)	13
NTRK2	1 (1.9)	1
NTRK3	31 (57.4)	6 (ETV6-NTRK3 most common, 46%)

- Company assumes distribution of tumour types in efficacy evaluable data set = clinical practice
- Distribution used to estimate a weighted set of outcomes in comparator arm → altering the distribution = big impact on ICER
- ERG & CDF clinical lead do not consider the distribution to be generalisable to clinical practice

Prevalence estimates by histology

Tumour site*	NTRK prevalence	Cases of NTRK per year (eligible population)
Colorectal	[redacted]	[redacted]
Non-small cell lung	[redacted]	[redacted]
Breast (secretory)	[redacted]	[redacted]
Sarcoma	[redacted]	[redacted]
Papillary thyroid (Not otherwise specified)	[redacted]	[redacted]
Salivary gland (MASC)	[redacted]	[redacted]
Neuroendocrine	[redacted]	[redacted]
Pancreatic	[redacted]	[redacted]
Gynaecological	[redacted]	[redacted]
Cholangiocarcinoma	[redacted]	[redacted]
Primary CNS (paediatric)	[redacted]	[redacted]
Infantile fibrosarcoma	[redacted]	[redacted]
Melanoma (paediatric)	[redacted]	[redacted]
Gastro-intestinal stromal tumours	[redacted]	[redacted]
Congenital mesoblastic nephroma	[redacted]	[redacted]

- Prevalence estimates derived from FMI (166k samples) dataset provided by company
- NTRK fusion prevalence estimate across all solid tumours = [redacted]
- ERG report that there are at least a [redacted] covered by the anticipated MA but not included in company's efficacy evaluable data set
- Plausible that NTRK gene fusions could potentially be present in 400+ tumour types
- Estimated patient numbers require assumptions about eligibility that will depend on treatment pathway
- Impacts on testing costs included in the model

** List not exhaustive*

Entrectinib positioning in treatment pathway

Tumour type	Positioning in the entrectinib clinical trial			Company's proposed positioning	NHSE & NHSI CDF Clinical Lead proposed positioning	NCRI-ACP-RCP-RCR suggested positioning
Line	Line, n					
	1st	2nd	3rd			
MASC	X	-	X	First-line	Agrees with company	Agrees with company
Soft-tissue sarcoma	X	X	X	First-line	First-line for chemo-resistant. Second-line for chemo-sensitive	Agrees for chemo-resistant Second-line for chemo-sensitive
Pancreatic	X	X	X	First-line	Uncertain, first- or second-line	First- or second-line
Cholangio-carcinoma	-	-	X	First-line	Uncertain, first- or second-line	Second-line +
Gynaecological	-	-	X	First-line	Second-line	Agrees with CDF lead
NSCLC	X	X	X	Second-line +	After any immunotherapy & 1st line cytotoxic chemo	First-line +
Breast	X	X	X	Second-line +	Third-line	Second-line +
Thyroid	X	X	X	Second-line +	Second-line	Second-line + (with more data could move to 1st line)
Colorectal	X	-	X	Second-line +	Third-line	Third-line +
Neuroendocrine carcinomas	X	X	-	Second-line +	Third-line	Second-line +

+ means and beyond

Comparator treatments

- Company not consistent between entrectinib's use in clinical trial and position of suggested comparators in company original submission
- Company's comparator dataset set drew predominantly from treatment options at later lines of therapy → does not consider line of therapy to be a prognostic factor
    - Did not provide a scenario analysis where the comparator data is matched to entrectinib's position in the clinical trials
    - Conducted subgroup analyses where [redacted]
- Company provided a scenario analysis where 2nd line treatments for breast, colorectal cancer and neuroendocrine tumours were removed from the analysis to reflect CDF clinical lead's preferred positioning (3rd line)
- ERG considered this scenario reasonable for decision making with the information available at this time

Technical team judgement

○ How entrectinib will be used in clinical practice remains a major uncertainty in the evidence base and can not be resolved at present

○ Data collection in the CDF is the only way to identify how TRK inhibitors will be used

○ Appropriate comparators will only be known once entrectinib's position is confirmed

Population and positioning

Issue	Resolved?
Prevalence of NTRK gene fusions **(Issue 1)**	At TE company agreed that the prevalence of NTRK gene fusions be sourced from the FMI data set 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 **(Issue 6)**	Clinical trial data is unlikely to represent the distribution of tumour sites seen in clinical practice. This could be addressed through further data collection in the CDF
Tumour sites unrepresented in the trial data **(Issue 7)**	Clinical trial data available for 13 tumour types but the eligible population covered by the anticipated MA is much wider. Clinical data could be collected in the CDF
Primary CNS and paediatric tumours **(Issue 8)**	At TE company included primary CNS and paediatric tumours in their base case population
Treatment pathway and positioning **(Issue 2)**	Entrectinib's position in the treatment pathway is currently unknown. Diagnostic testing strategy will likely impact on where entrectinib is used in the treatment pathway. Information about positioning/commissioning criteria needed
Comparator treatments **(Issue 11)**	Comparator treatments are uncertain until entrectinib's position in the treatment pathway is known

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

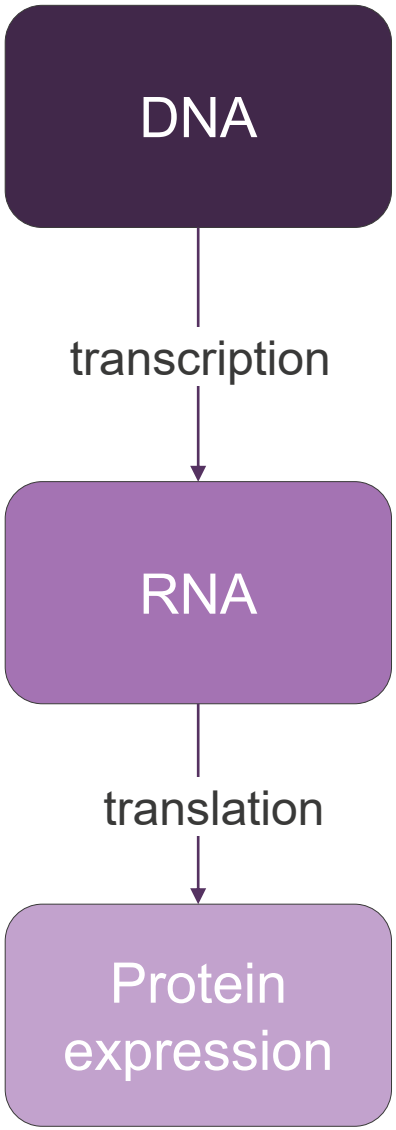
Screening populations

Tumour site	Cancer incidence per year (England), stage III/IV	NTRK fusion incidence per year
Colorectal	19,154	XX
Non-small cell lung	18,568	XX
Breast (secretory*)	6,916	XX (X)
Sarcoma	877	XX
Thyroid	1,008	XX
Salivary gland (MASC*)	2	X (X)
Neuroendocrine	2,312	X
Pancreatic	6,543	XX
Gynaecological	3,535	X
Cholangiocarcinoma	334	X
Primary CNS (glioma)	2,848	XX
Infantile fibrosarcoma	30	XX
Melanoma	1,393	X
Total (including other tumour sites with NTRK)	**97,247**	XXX

- NHS England suggests screening based on diagnosis of Stage III/IV cancer (approximately 100k patients per year)
- WGS is already available for paediatric indications and sarcomas
- RNA-based NGS is already used in clinical practice in a subgroup of NSCLCs

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

Genomic testing

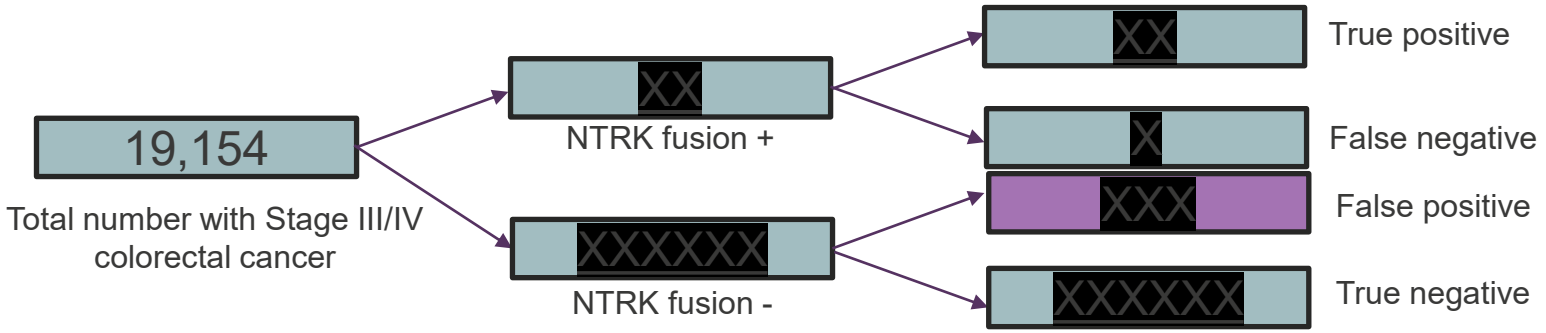


- NHS England suggest DNA/RNA-based NGS:
  - DNA can reliably find targeted panels with >70% sensitivity and very high specificity and can be added to existing gene panels at minimal cost
  - However DNA cannot easily find new fusion partners and may have difficult identifying NTRK2/3 gene fusions
  - 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

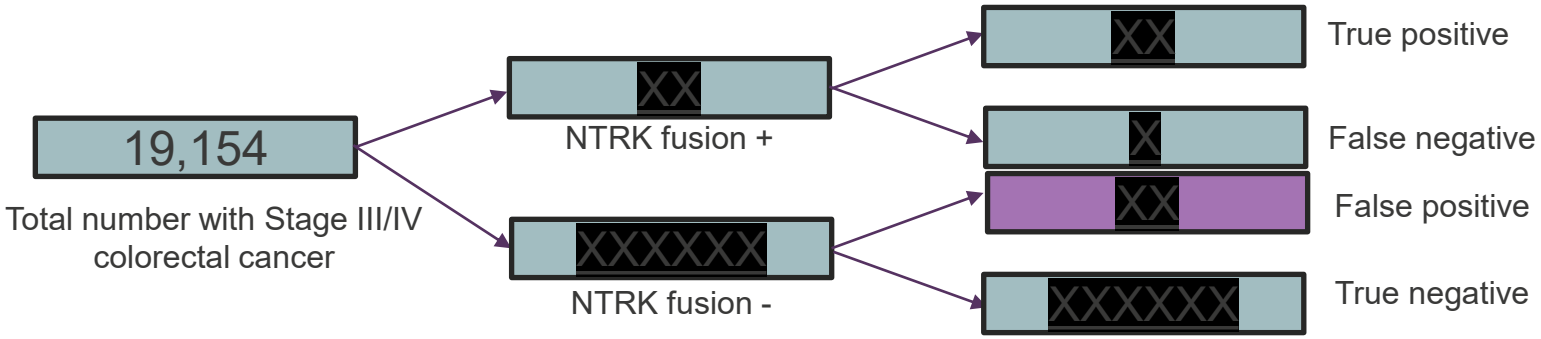
- For low prevalence tumour sites, diagnostic accuracy needs to be very high in order to avoid false positive results – for these patients, the tumour would not be expected to respond
- Below is a worked example using NTRK fusion prevalence estimate for colorectal cancer, literature values for sensitivity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

Prevalence	XXXX%
Sensitivity	81%
Specificity	**99.0%**



17% chance of positive identification being true

Prevalence	XXXX%
Sensitivity	81%
Specificity	**99.9%**



67% chance of positive identification being true

Company's hierarchical screening approach

- Company includes a two-step screening approach → immunohistochemical (IHC) test followed by a next generation sequencing (NGS) test if IHC is positive (11% of samples)
- Screening conducted at entrectinib's expected position in the treatment pathway
- ERG considers this approach broadly plausible
- Company considers the optimal testing route to be wide-scale implementation of appropriate NGS-based testing as early in the treatment pathway as possible
    - CDF clinical lead and NCRI-ACP-RCP-RCR agree

Technical team judgement

○ The screening pathway depends on the provisions set up by NHS England in a timeframe that aligns with this appraisal

○ Recognise that this is a rapidly changing field

○ If recommended in the CDF, this will be a key issue when entrectinib exits

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

	Company	ERG
Testing available that identifies NTRK fusions	No costs included	Confirmatory NGS test following WGS
Other genomic testing already available	Entrectinib arm: IHC cost (£75) and confirmatory NGS test (£XXX) Comparator arm: IHC cost	Entrectinib arm: IHC cost (£75) and confirmatory NGS test (£XXX) • NGS cost not included for lung cancer Comparator arm: no costs
No other genomic testing available	Entrectinib arm: as above Comparator arm: no cost	

- **The ERG** consider that until NHS England implements this diagnostic overhaul, screening pathways for each tumour site should be modelled and costed
- **NHS England** consider that all companies that benefit from this new service provision should provide a proportion of the costs

Diagnosis

Issue	Resolved?
NTRK gene fusion 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
Testing costs (Issue 4)	NICE methods guide was not designed to address a system-wide overhaul in diagnostic techniques. Cost of testing will depend on the testing strategy implemented by NHS England and risk sharing agreement between the company and NHS England
Identification of NTRK gene fusions (Issue 5)	Diagnostic accuracy is currently unknown. Given the rarity of the NTRK gene fusion in some tumour types, there are big consequences for small differences of diagnostic accuracy

Heterogeneity – company position

- Company assumes that each of the solid tumour types will have identical response rates when treated with entrectinib (homogeneity of response) → does not account for the potential heterogeneity of response across different tumour types or unrepresented tumour sites
- Company use a pooled response estimate across each of the tumour types included in their efficacy evaluable dataset, XX% response
- Do not consider subgroup data for entrectinib robust enough at the specific tumour type level for reliable modelling to assess tumour or response heterogeneity

Bayesian Hierarchical Model - response

Tumor Type	N	Responders
Overall	[redacted]	[redacted]
Sarcoma	[redacted]	[redacted]
NSCLC	[redacted]	[redacted]
CRC	[redacted]	[redacted]
Neuroendocrine tumours	[redacted]	[redacted]
Pancreatic	[redacted]	[redacted]
Gynaecological	[redacted]	[redacted]
Cholangiocarcinoma	[redacted]	[redacted]
MASC	[redacted]	[redacted]
Breast	[redacted]	[redacted]
Thyroid	[redacted]	[redacted]
CNS Primary	[redacted]	[redacted]
Paediatric CNS Primary	[redacted]	[redacted]
Paediatric (non-CNS)	[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

Bayesian Hierarchical Model - output

- Estimated mean response rate across all tumour types is [redacted] (95% CI: [redacted]) from BHM → similar ORR to company's original submission with homogeneity assumption, [redacted] 95% CI: [redacted])
- Predictive probability of response for unrepresented tumour types is [redacted] (95% CI: [redacted])
- Distributions of response for [redacted] suggest that response rates [redacted]% are plausible

Figure removed commercial in confidence

- Tumour sites with high prevalence of NTRK gene fusions have [redacted] response rates

Bayesian Hierarchical Model

- Unclear how heterogeneity in response outcomes impacts on survival outcomes
- Heterogeneity in time to event outcomes (PFS and OS) can also be explored using the BHM framework
- ERG note that survival data may be too immature currently and small population within each tumour type may limit the usefulness of results at present, company agrees
- NCRI-ACP-RCP-RCR note that it is currently uncertain whether responses would be heterogenous and proposed additional modelling and data collection are appropriate
  - Clinical expert opinion suggests that inhibition of a signalling pathway, and response to treatment, being driven by a genomic fusion may be more homogeneous than treatment for a somatic fusion

Technical team judgement

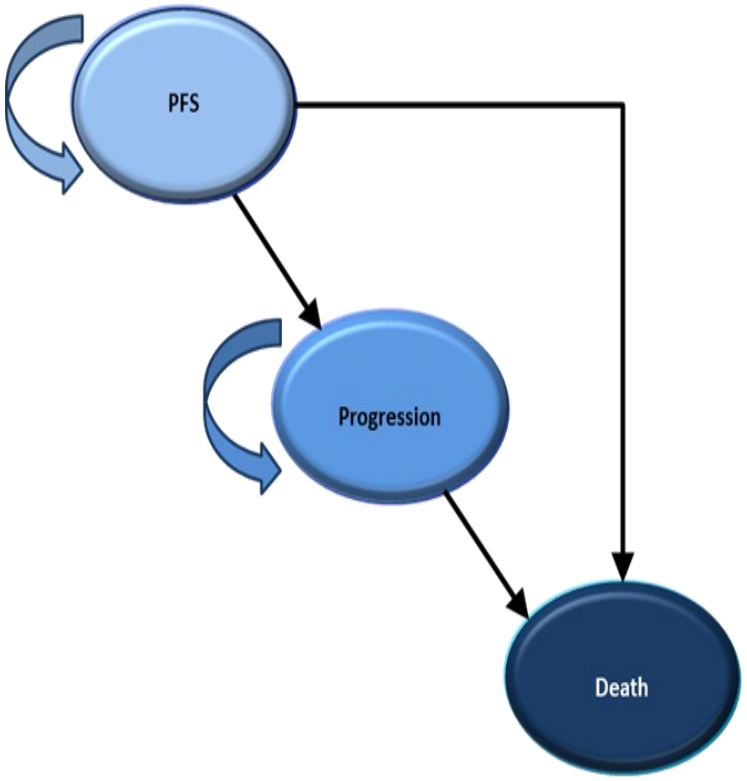
○ Considerable uncertainty about the company's assumption of homogeneous treatment effect across tumour sites due to the lack of supporting evidence

Heterogeneity

Issue	Resolved?
Heterogeneity of response across different tumour sites **(Issue 9)**	BHM provides a framework for assessing heterogeneity of response. This framework is used to generate inputs for response-based model structure. Response data can be partially collected in the CDF
Heterogeneity of survival outcomes PFS and OS across different tumour sites **(Issue 9)**	Survival data are currently immature. Data could continue to mature in the CDF

Company's model structure: partitioned survival model with historical comparator

- Three state partitioned survival model: progression-free, progressed and dead
- Entrectinib clinical trials = single arm trials
- Comparator data (PFS and OS) sourced from NICE approved comparators for each of the tumour types represented in the entrectinib clinical trials
- Median PFS and OS were averaged and then pooled to give the mean overall PFS and OS across all tumour types, weighted by the distribution of each tumour type in the trial population
- Where data were not available from NICE recommended treatments, an average from the other tumour types was used
- Unrepresented tumour types are not accounted for in company's model
- Company's model produces a single ICER



Company's historical comparator structure

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Treatment arm:

- PFS and OS curves represent observed survival of entire efficacy evaluable population
- No ability to adjust or compare the population based on any potential heterogeneity issue (most populations are too small to consider on their own)
- Therefore assumes homogeneous response to treatment and homogeneous natural history of every tumour type

Comparator arm:

- Mean PFS and OS for each tumour type, used exponential extrapolations for each and weighted by tumour type in the efficacy evaluable population to create this curve

Company's confirmatory analysis: previous line of treatment

- Time to next treatment (TTNT) survival curve generated based on XXXXXXX from the STARTRK-2 trial
- TTNT used as a proxy for PFS
- Results gave a median TTNT of XXX months which the company considered similar to the XXXX months estimated in the historical comparator pooled treatment effect
- Company did not include this analysis in their economic model

- ERG considered this approach to be promising but it relies on several assumptions:
  - the benefit of treatment is in delaying disease progression
  - survival risk is treatment independent
  - mortality risk pre-enrolment into the trial was negligible

ERG's exploratory model structure: response-based model

- ERG considered the response-based analysis an appropriate alternative to the company's approach
- Response-based model uses effectiveness data on non-responder patients as a proxy for patients not receiving active treatment (comparator)
- Survival in entrectinib arm was estimated as the weighted average of survival in the responder and non-responder patients, weighted by the estimated response rate of XX% from the BHM → possible to adjust response rates with this approach
- Approach requires the assumption of a surrogate response between response rates and time-to-event outcomes

Response-based model output

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Technical team judgement

- Each model structure has biases
- Possible to collect data in the CDF to better inform all 3 model structures, and observe if they product similar estimates

Utility values

- EQ-5D-3L collected in STARTRK-2 trial → trial derived value used for pre-progressed health state but company considered progressed disease health state value implausible
- Comparator utility values extracted from NICE technology appraisals for each tumour type and the weighted average used for each health state

Company utility values

Pre-progressed health state		Progressed health state	
Entrectinib	SoC	Entrectinib	SoC
[redacted]	0.73	0.59	0.59

- Differential utility value in pre-progressed health state justified given the oral administration of entrectinib (more convenient) and relatively tolerable safety profile compared with cytotoxic chemotherapies
- ERG consider the progressed health state utility value to be plausible but lack of evidence to justify differential quality of life and magnitude of the difference in the pre-progressed health state
- ERG concerned company's choice of source NICE technology appraisal may produce bias → e.g. selected utilities vary by line of therapy
- NHS England and NHS Improvement National Clinical Lead for the Cancer Drugs Fund considers it appropriate to use same utility value in pre-progressed health state

Technical team judgement

○ Have not seen substantive evidence to support the magnitude of the difference in the pre-progressed utility value between arms. Company and ERG base-case including the differential utility values biases the results in favour of entrectinib

Prognostic factors

- All people included in the entrectinib trials were NTRK fusion positive and 20.4% of the entrectinib efficacy evaluable population had CNS metastases
- Unknown how prevalent CNS metastases are in comparator arm and only small proportion likely to be NTRK fusion positive
- Limited evidence available that shows NTRK gene fusions are prognostic
- Company provides scenario analyses adjusting for these prognostic factors
- ERG highlight that other prognostic factors have not been accounted for, for example ECOG score
- NCRI-ACP-RCP-RCR note insufficient data to determine impact of the presence of CNS metastases on prognosis in the NTRK fusion population

Technical team judgement

○ Not appropriate to adjust for poorer prognosis when tumours are NTRK positive as no evidence to support this

○ Appropriate to adjust for factors known to impact on prognosis

Modelling (1)

Issue	Resolved?
Constructing a comparator arm **(Issue 10)**	Different approaches taken to constructing a comparator arm in each of the model structures, each with limitations
Model structure **(Issue 14)**	Each model structure has associated uncertainty. If the outputs concur then that could reduce uncertainty. Data collection in CDF may inform model choice
Subsequent therapies **(Issue 13)**	Company modelled XXX of people in entrectinib arm receive subsequent therapies and implemented a 6 month treatment duration at TE. Some outstanding uncertainty around treatments given as subsequent therapies due to uncertainty around position of entrectinib in the treatment pathway. Could be resolved through further data collection in the CDF
Utility values **(Issue 19)**	Company considers a differential utility value in the pre-progressed health state to be justifiable based on ease of administration and relatively tolerable safety profile. Company and ERG base-case including the differential utility values biases the results in favour of entrectinib

Modelling (2)

Issue	Resolved?
Prognostic factors **(Issue 12)**	Outstanding uncertainty in the analysis that comparator arm is unadjusted for CNS metastases in company and ERG base case
Survival extrapolation **(Issue 15)**	Very limited data available for overall and progression-free survival. Different approaches taken by company and ERG with notable impact on the ICER. Longer term survival data will help resolve some uncertainty
Drug wastage and source of treatment costs **(Issue 16)**	At TE company ran a scenario including drug wastage. ERG included in ERG base case. Moderate increase to company's base case ICER
	At TE company ran a scenario using eMIT costs instead of BNF to source comparator treatment costs. ERG included in ERG base case. Small decrease to company's base case ICER
	Original company submission assumed 100% dose intensity for entrectinib as a conservative assumption. Mean observed dose in original analysis (31st May 2018) was XXXXX. Applying the mean observed dose intensity for entrectinib decreases the company's updated base case ICER by around £4,500 (£44,897 instead of £49,358). Company suggest that drug wastage is negated by reduced dosing intensity

Modelling (3)

Issue	Resolved?
Administration costs and resource use **(Issue 17)**	Company did not run an analysis with individual administration costs for each of the comparator treatments = an outstanding uncertainty with unknown but likely minimal impact on ICER
	At TE company ran a scenario including oral chemotherapy tariff in both arms. ERG included in ERG base case. Moderate increase to company's base case ICER
	At TE company ran a scenario including monitoring costs in progressed disease health state. Small increase to company's base case ICER

Company base case

- Including entrectinib PAS and list price for all other treatments

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (per QALY gained)
With testing costs included							
Established management	£61,228	1.61	1.03	[redacted]	[redacted]	[redacted]	£49,358
Entrectinib	[redacted]	[redacted]	[redacted]				
Without testing costs included							
Established management	£21,208	1.61	1.03	[redacted]	[redacted]	[redacted]	£35,770
Entrectinib	[redacted]	[redacted]	[redacted]				

ERG base case

- Including entrectinib PAS and list price for all other treatments
- Updated estimate of number requiring confirmatory testing and incidence of thyroid tumour
- Includes CDF Clinical Lead's updated positioning and oral chemotherapy tariff

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (per QALY gained)
With testing costs included							
Established management	£19,209	1.59	1.02	[redacted]	[redacted]	[redacted]	£79,391
Entrectinib	[redacted]	[redacted]	[redacted]				
Without testing costs included							
Established management	£19,209	1.59	1.02	[redacted]	[redacted]	[redacted]	£40,778
Entrectinib	[redacted]	[redacted]	[redacted]				

ERG exploratory analysis

Scenario	Total inc. costs	Total inc. QALYs	ICER
Updated company base case post-TE	[redacted]	[redacted]	£49,358
1. Weibull distribution for OS and PFS	[redacted]	[redacted]	£62,750
2. Comparator arm not including testing costs if do not identify NTRK fusions	[redacted]	[redacted]	£60,234
3. Removal of testing costs for NGS for lung cancer	Can't be applied to company base case		
4. Confirmatory RNA-based NGS test after WGS	[redacted]	[redacted]	£50,593
5. Testing costs estimated using NNS based on whole NTRK population	Can't be applied to company base case		
6. Six months subsequent therapy treatment duration	[redacted]	[redacted]	£39,890
7. eMIT costs as the source of comparator costs	[redacted]	[redacted]	£49,103
8. Inclusion of drug wastage	[redacted]	[redacted]	£52,103
9. ERG's revised estimation of number requiring confirmatory testing and updated incidence of thyroid tumour	[redacted]	[redacted]	£49,539
10. Removal of inappropriate comparators	[redacted]	[redacted]	£49,294
11. Inclusion of oral chemotherapy tariff cost	[redacted]	[redacted]	£51,491
12. Revised cost of progressed disease health state	[redacted]	[redacted]	£49,647
Technical team base case	[redacted]	[redacted]	**£79,330**

Implementation and training (Issue 18)

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**

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

- What additional training will be required?
  - Oncologists: new concepts associated with tumour-agnostic therapies → eligible tumour types, diagnostic pathway, position in treatment pathway, safety profile, collection of tissue sample
  - Pathologists: material handling
- Any prescribing considerations?

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

Innovation (Issue 22)

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**

Company highlighted:

- **Step change** in cancer treatment → focus on underlying oncogenic marker, regardless of histology and CNS-active NTRK inhibitor
- Novel genomic technologies to identify NTRK fusion positive solid tumours provides **wider benefits to patient health and cost efficiencies for health care systems** as multiple different actionable targets can be identified, even if NTRK fusion negative → clinical trial availability or other targeted therapy

Technical team consideration:

- **Newly identified rare gene fusion** that occurs in a **wide range of tumour types**
- **High response** over a **wide range of tumour types**
- **First site-agnostic treatments** to be appraised by NICE
- May represent a **step change** in cancer treatment, but **lack of evidence** of demonstrable and distinctive benefits of a substantial nature which **may not have been adequately captured** in the reference case QALY measure
- **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

End of life (Issue 21)

- 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
- The assumptions used in the reference case economic modelling are plausible, objective and robust

- 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

End of life: life expectancy

Tumour site	Meet life expectancy? ERG base case, mean months	Annual eligible population*
Colorectal	13.08	XX
Non-small cell lung	15.36	XX
Breast	17.56	XX
Sarcoma	20.63	XX
Thyroid	44.65	XX
Salivary gland (MASC)	19.91	X
Neuroendocrine	57.14	X
Pancreatic	12.70	XX
Gynaecological	NR	X
Cholangiocarcinoma	24.86	X
Primary CNS	11.46	X
Infantile fibrosarcoma	24.86	X
Melanoma	9.23	X

- Using estimated mean overall survival from the modelled comparator data shows that most tumour sites meet life expectancy criteria
- Thyroid and neuroendocrine tumours account for XX% of the annual NTRK eligible population

*shown are those included in the clinical trials but total eligible population n=194

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

Administration issues

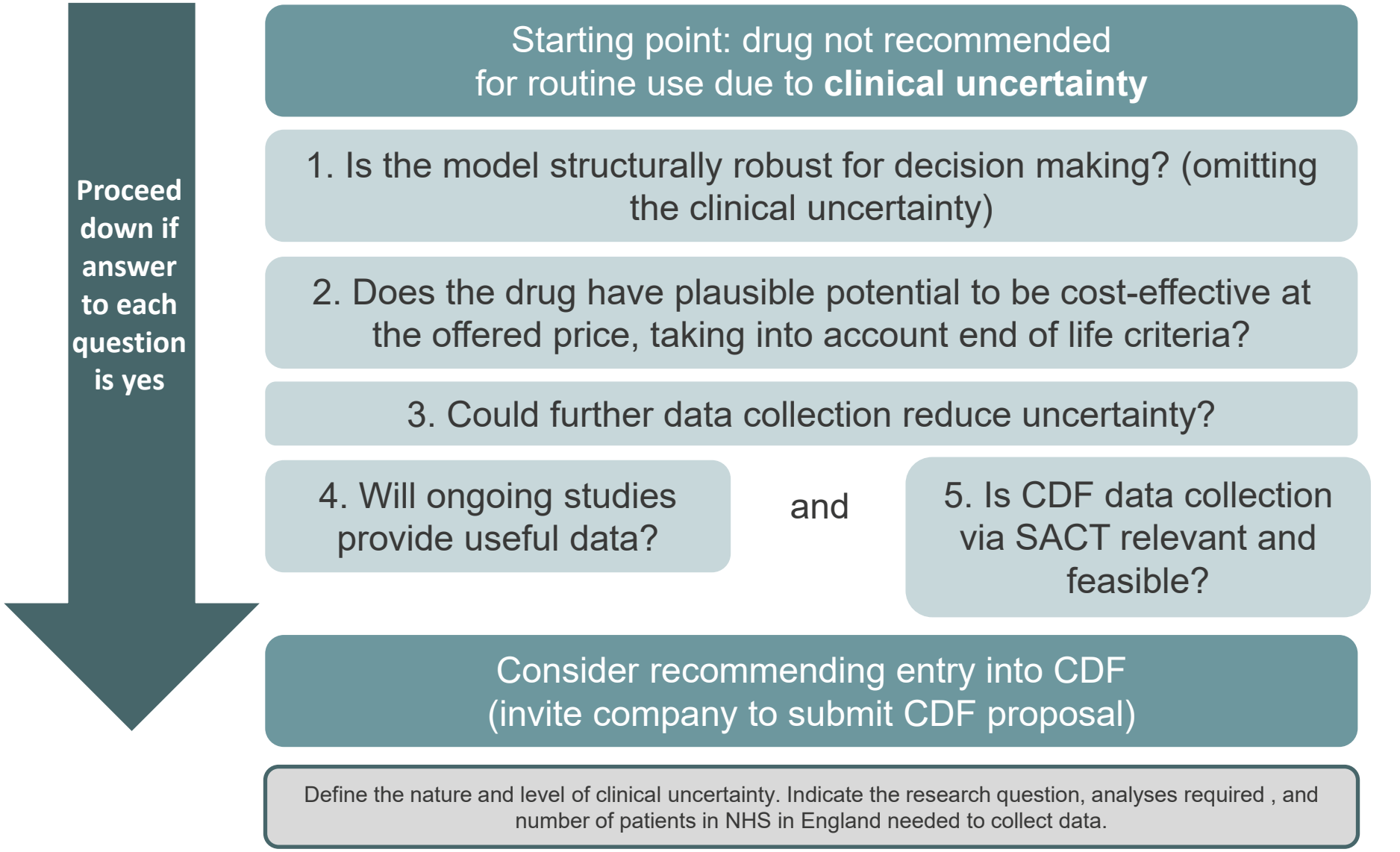
- Oral administration so only people able to swallow able to have treatment

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

CDF recommendation criteria



NICE

- Does entrectinib meet the criteria for entry into the CDF?

CDF – Potential data sources

Data source	Summary; See draft Data Collection Agreement for further details
Ongoing clinical trials	• Further patient recruitment and more mature data • Interim reports: TBC, [redacted] • Final datacuts: [redacted] (STARTRK-2) and [redacted] (STARTRK-NG) • [redacted]
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'
[redacted]	• [redacted] • [redacted] • [redacted] • [redacted]
[redacted]	• [redacted] • [redacted] • [redacted] • [redacted]
[redacted]	• Overlap with RWE that could be collected within CDF • Currently in early exploratory stage

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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+6	Prevalence + distribution of NTRK	CDF-RWE
2+7	Generalisability of the trial	CDF-RWE
3+4	Screening pathway, testing costs	CDF-RWE
5	Diagnostic accuracy	
9	Heterogeneity of response	Trial; [redacted]
11	Robustness of control arm	[redacted]#
13	Subsequent therapies	CDF-RWE
19	Pre-progression utility state	[redacted]%
21	EoL criteria	CDF-RWE; [redacted]
23	Immaturity of the data	Trial

* Multiple other sources may provide supportive evidence

\# [redacted]

% [redacted]