NICE National Institute for Health and Care Excellence

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

ACM2 – Chair's presentation

Chair: Gary McVeigh

NICE technical team: Adam Brooke, Christian Griffiths, Linda Landells

Company: Bayer

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Key consultation response issues

- Heterogeneity of response
  - Inclusion of the Bayesian Hierarchical Model
- Survival extrapolation
  - Post-progression survival estimation
  - Post-progression treatment costs
  - Potential cure for paediatric patients
- Utility values
  - Post-progression utility values
  - Pre-progression utility values

[redacted]

Larotrectinib (Vitrakvi, Bayer)

Recommendation in the ACD:

Larotrectinib is not recommended 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

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

[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]

Summary committee conclusions – clinical evidence

Topic	Conclusion	ACD
NTRK gene fusions	Better characterisation of NTRK gene fusions is needed to fully support the histology independent approach	3.2
Treatment pathway	Larotrectinib is positioned last-line so that it does not displace any effective therapies. Further information is being collected to determine how larotrectinib would be used in clinical practice	3.5
Diagnosis of NTRK gene fusions	NHS England is currently establishing a national service for cancer genomic testing. The diagnostic testing pathway is uncertain until NHS England's plans are fully established	3.7
Generalisability of clinical evidence	Key clinical evidence is not generalisable to NHS clinical practice because of the distribution of tumour types and the unknown effect of patient characteristics	3.10
Survival data	Immaturity of the survival data meant that the size of larotrectinib's benefit could not be reliably estimated	3.11
Heterogeneity of response	Bayesian Hierarchical modelling moderates influence of extreme results and reduces overall response rate from 72% to 57%. It is a useful tool for exploring heterogeneity	3.14
Primary CNS tumours	Primary CNS tumours have lower response to larotrectinib, primary CNS data should be included in analysis	3.15

[redacted]

Summary committee conclusions – economic modelling

Topic	Conclusion	ACD
Response to larotrectinib	The company model assumes equal response for all tumour types and fusion types. This is inappropriate, and adjustment should be made for potential differences by subgroup.	3.13
Model structure	3 approaches to creating a comparator population were used, each one likely introduced bias to the analysis. Outputs of all 3 models can be considered	3.16 3.17
Effect of a cure	Some paediatric patients were included that would have survived without larotrectinib, but this was not modelled. This could strongly bias in favour of larotrectinib.	3.19
Survival extrapolation	Model output was extremely sensitive to choice of survival extrapolation, unable to trust the results	3.20
Post-progression survival	Survival after progression was implausibly greater than survival before progression, the concept of high depth of response for these patients is speculative because data is immature	3.22
Utility values	Utility values should be equal post-progression and a scenario should be provided with equal pre-progression utility	3.23 3.24
Cost of post-progression treatment	Larotrectinib was used after progression for some patients, this issues has not been fully explored	3.28

Summary committee conclusions – decision

Topic	Conclusion	ACD
End-of-life considerations	Larotrectinib has plausible potential to meet NICE's end of life criteria but there are many challenges with the data and uncertainty	3.29
Cancer Drugs Fund	Larotrectinib does not have potential to be cost-effective and some key uncertainties were unlikely to be resolved with the proposed data collection	3.31
Innovation	Larotrectinib is innovative because it represents a major change in treatment of NTRK fusion-positive solid tumours but there are not additional benefits not captured in the QALY measurement	3.32
Equality considerations	There are no equality issues relevant to the recommendations	3.33

[redacted]

ACD consultation

Contributing consultation comments

- Company (Bayer)
  - Do not present additional evidence
  - Provide an updated patient access scheme discount
  - Provide consultation comments response
- Professional Groups
  - RCP joint response
  - Roy Castle Lung Cancer Foundation
- Patient Groups
  - GIST Support UK
- Clinical experts
- NHS England CDF clinical lead

[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]

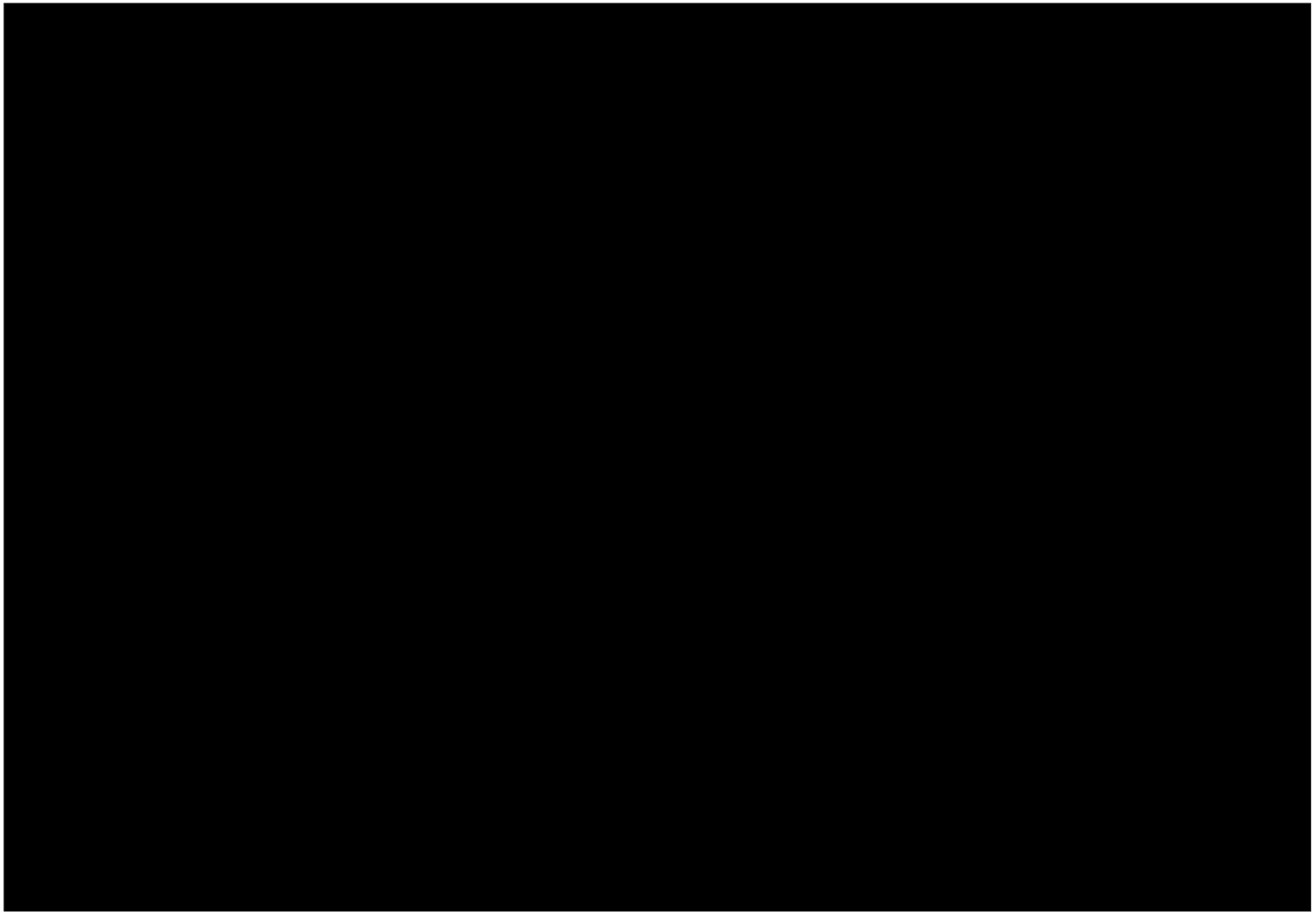
Bayesian Hierarchical Model - response

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



Heterogeneity – company response

ACD committee conclusion:

- *'…given the observed differences in response and poor characterisation of NTRK gene fusions and fusion partners, assuming equal response [is] inappropriate'*
- *'Bayesian Hierarchical Modelling (BHM) was a useful tool for exploring heterogeneity in response to larotrectinib'*

Bayer:

- Further data collection with the CDF will provide additional insight into response rates in tumours identified as being suitable for larotrectinib in clinical practice
- Bayer believe decision making should not be based solely on the BHM because it quotes the ERG that the analysis is 'exploratory and requires strong assumptions about the link between response and survival outcomes'
- **NB: This quote refers to assessment of heterogeneity in time-to-event outcomes performed by the ERG and not heterogeneity of response.**
- Bayer consider the BHM represents a 'worst case scenario'

[redacted]

Heterogeneity – CDF clinical lead comments

- NHS England remain concerned with generalisability to NHS clinical practice because *** of the 93 patients with non-CNS solid tumours had no prior systemic therapies
- A high proportion of tumour types in the trials were in uncommon/rare tumour types that would not be seen as CDF entrants (e.g. soft tissue sarcoma, infantile fibrosarcoma)
- Relatively few patients with common tumour types such as NSCLC and colorectal cancer
- There is a biologically plausible case that in cancers which are much more frequently driven by NTRK gene fusions would have higher response rates and greater benefits
- The CDF is ideally placed to provide data across the complete spectrum of malignancies but first the company must present the committee with a plausibly cost effective ICER

[redacted]

Post-progression survival – company response

ACD committee conclusions:

- *'Post-progression survival estimates were implausible'*
- *'Committee considered [a high depth of response] to be speculative because the current evidence base was very immature. It also noted the TRK-inhibitor resistance mechanisms were not well characterised and would not explain the size of the discrepancy.'*

Bayer:

- There is precedent for impressive survival benefits with targeted therapies. For example:
  - Imatinib for chronic myeloid leukemia (3 to 4x increase in OS) and GIST
  - Immunotherapy agents in HER2+ breast cancer and NSCLC
- 'Early tumour shrinkage' and 'depth of response' are correlated to survival outcomes for:
  - Any treatment in metastatic colorectal cancer
  - ALK inhibitors or PD-L1 antibodies in NSCLC
  - Any treatment in unresectable metastatic melanoma
- Therefore, Bayer ask committee to reconsider the preferred assumptions around post-progression survival scenarios as the differential has a biologically plausible mechanism
- The concept of depth of response relating to survival outcomes was validated with 3 clinical experts, all agreed that the modelled survival benefit was clinically plausible

[redacted]

Post-progression survival

[redacted]

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

Approximately [redacted] times survival gain difference between larotrectinib and weighted comparator post progression

[redacted]

Post-progression treatment costs – company response

ACD committee conclusion:

- *'Some patients continued to have larotrectinib after progression'*
- *'The costs of larotrectinib post-progression should be included but this issue has not been fully explored'*
- *'A high proportion of patients [had] and experimental treatment (LOXO-195) that would not be used in clinical practice…The committee considered it appropriate to adjust for the benefits of these treatments'*

Bayer:

- A scenario was provided whereby time to treatment discontinuation extrapolation curves were used as an alternative method to model larotrectinib costs

- A total of [redacted]/37 progressed patients continued to receive larotrectinib after the point of progression. Bayer have not provided duration of treatment for these patients with extended larotrectinib treatment so it is not possible to estimate costs for the entire cohort or consider which patients could benefit from continued larotrectinib.
- A total of [redacted]/37 progressed patients received the experimental treatment LOXO-195 with unknown costs and benefits

[redacted]

Potential cure for paediatric patients – company response

ACD committee conclusion:

- *'The current model structure captured the benefit of any cure in the Kaplan-Meier survival analysis in the larotrectinib arm but did not model the possibility of a cure in the comparator arm'*
- *'model structures proposed were not appropriate for a heterogeneous population…a different model structure should be used to explore the effect of a cure'*

Bayer:

- Bayer believe this conclusion is not supported by the evidence
- The possibility of a cure in the comparator arm is only for a minority of patients with infantile fibrosarcoma, most patients had advanced or metastatic solid tumours.
- It is a requirement of the license that patients have no satisfactory treatment options, therefore the likelihood of a cure in the remainder of the comparator arm is very low
- Bayer have conducted analysis removing patients with IFS/ paediatric sarcomas and this makes minimal difference to the ICER (-1.6% to +3.2%). **NB: This analysis does not remove the survival benefit of these patients from the KM curves or extrapolations**
- Bayer believe the added benefits of limb-sparing, non-mutilating surgery for primary disease post larotrectinib were unaccounted for in the analysis

[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 [redacted] 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]

Potential cure for paediatric patients – company response

Survival estimates - CDF clinical lead comments

- A depth of response may credibly explain some of the post-progression survival increment but there is no evidence presented by the company to justify the extent of post-progression survival
- All examples provided by the company are following first line chemotherapy in diseases in which there are commissioned second line (and beyond) therapies. Much of the increased post progression survival could be explained by the better performance status of patients following a greater depth of response and thus their better ability to go onto further treatment. But such a scenario will not apply post-larotrectinib as there are no further treatments as larotrectinib is the 'last line' of treatment
- Use of larotrectinib post-progression was common in the trials, different scenarios are needed to establish the effect of different duration of treatment
- Post-progression survival may be biased by patients who potentially have surgical options as salvage therapy and constitute a high proportion of patients in the dataset
- In fibrosarcoma, cures are common with conventional management but so is the need for amputation and thus larotrectinib has a potentially valuable role in the treatment of infantile fibrosarcoma in avoiding the need for amputation.

[redacted]

Post-progression utility – company response

ACD committee conclusion:

- *'there was no plausible reason why post-progression utility would be so much higher for larotrectinib than the comparator for the entire population'*
- *'a scenario with equal post-progression utility values for larotrectinib and the pooled comparator… was more appropriate'*

Bayer:

- Quality of life may be better for patients with larotrectinib because:
  - Lack of ongoing toxicity from radiotherapy or chemotherapy
  - A reduction in tumour burden at the point of progression
- There is precedent in the literature for high post-progression utility values in immunotherapies

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

NB: The weighted comparator treatment is best supportive care for most cancer types or, potentially, non-satisfactory chemotherapy treatments

[redacted]

Pre-progression utility – company response

ACD committee conclusion:

- *'any difference in pre-progression utility values would represent positive effects from reduced tumour size'*
- *'it is appropriate to do sensitivity analysis on the pre-progression utility values to see the effect of assuming equal values for larotrectinib and the pooled comparator'*

Bayer:

- Bayer have not provided this sensitivity analysis
- 'Early tumour shrinkage' and 'depth of response' are associated with improvements in quality of life for metastatic colorectal cancer and metastatic breast cancer
- Inpatient care with chemotherapy requires management of toxic effects vs outpatient management with larotrectinib, allowing patients to attend school and work

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

[redacted]

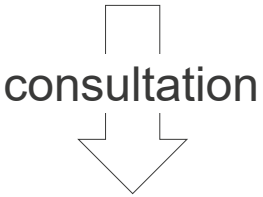
Professional group, patient group and clinician comments on ACD

- RCP – This appraisal does not fully address the key issue of testing – NICE needs to consult directly with Genomics England and Genomics Hubs. NICE needs to consider the feasibility and cost of testing
- RCP – Question the ability of Bayesian and other statistical assessments to evaluate the benefit of larotrectinib. Commonly used assessment methodology may not be suitable to assess benefit – clinically there is no doubt that this is an effective treatment.
- RCP – Genomic data available are limited and further description of the biology of NTRK fusions is essential to the continuing discussion
- Roy Castle Lung Cancer Foundation – disappointed that the committee did not recommend larotrectinib as it represents a new molecular target. Whilst data matures, larotrectinib would be available to appropriate patients via the CDF
- GIST support UK – Use of the CDF will provide access to those who need it while gathering the data needed
- Company nominated expert – CDF and SACT databases are ideal for this type of assessment, to assess real population benefits. It would be better to do this in an NHS umbrella rather than a company sponsored one
- Clinical expert – The recommendation biases against children with incurable advanced NTRK fusion-positive cancers who have no satisfactory treatment options

[redacted]

Change in PAS after consultation

ACM1 cost per 30-day supply		
List price	Percentage discount	Discounted price
£15,000	[redacted]	[redacted]



ACM2 revised cost per 30-day supply		
List price	Percentage discount	Discounted price
£15,000	[redacted]	[redacted]

[redacted]

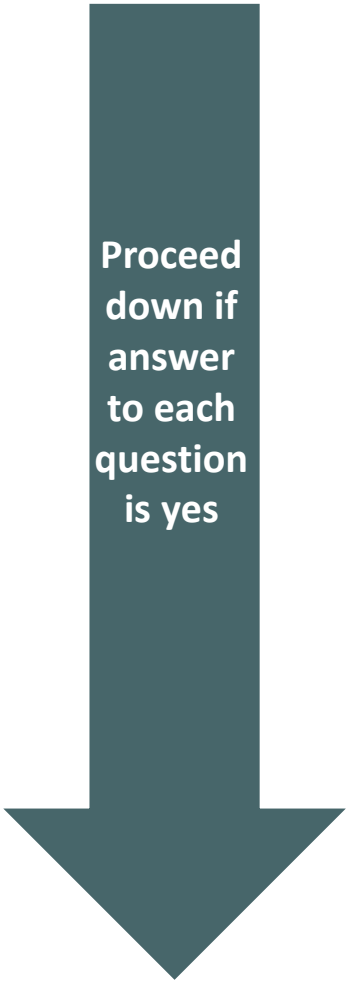
Cost-effectiveness results

- ERG corrected the cost-effectiveness results submitted with the updated PAS
- Post-ACM1 scenario requested from the ERG:
  - ERG partitioned response model with overall response rate of 57% (output of BHM)
  - Oral chemotherapy administration costs included
  - Drug wastage costs included
  - Post-progression utility independent of treatment ([redacted] for both treatment arms)
  - Testing costs included (assumed to be NHS England's proposed cost)

Scenario	Company calculated ICER	ERG corrected ICER
1. Company base case	£16,155	£16,155
2. 1 + committee preferences above	£29,077	£30,888
3. 2 + Post-progression survival equivalent for larotrectinib and comparator	£45,111	£48,161
4. 2 + post-progression survival for larotrectinib equivalent to overall survival for comparator	£37,933	£40,342

[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]