NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document** from Bayer
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3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. GIST Support UK
   b. Roy Castle Lung Cancer Foundation
   c. Joint response from the Royal College of Physicians
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4. **Comments on the Appraisal Consultation Document from experts:**
   a. Dr Alistair Reid – clinical expert, nominated by the Royal College of Pathologists
   b. Dr Harpreet Wasan, Consultant Oncologist – clinical expert, nominated by Bayer

There were no Appraisal Consultation comments submitted through the NICE website.

5. **Evidence Review Group critique of company comments on the ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Larotrectinib for treating advanced solid tumours with TRK fusions [ID1299]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	Bayer	Bayer are disappointed that larotrectinib for advanced neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours in adults and children who have no satisfactory treatment options has not been recommended for use within the Cancer Drugs Fund (CDF). Bayer recognises the challenges and uncertainties associated with appraising the first histology independent cancer treatment in Europe. Bayer also specifically acknowledge the uncertainty in modelling survival outcomes with immature data when there have been so few deaths in the study programme. Larotrectinib has demonstrated efficacy across a diverse group of tumours and age groups, ranging from one month to 79 years, all with the common feature of harbouring an NTRK gene fusion. As well as high response rates (72%), larotrectinib induced rapid and durable responses, with median time to response of 1.8 months in a population of heavily pre-treated patients, as well as a median of the maximum percentage shrinkage of tumour size of 66% (1). Indeed, the EPAR states '***the efficacy estimates available today may be considered outstanding in this generally late stage disease setting'*** (1). As a result of the early onset of clinical benefits, the degree of tumour shrinkage and the favourable safety profile, rapid and sustained clinically meaningful improvements in quality of life were observed with larotrectinib (2). A case study demonstrating the relationship between speed of response and depth of tumour shrinkage and the corresponding impact on symptoms of the disease is illustrated below	Thank you for your comment. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF.

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			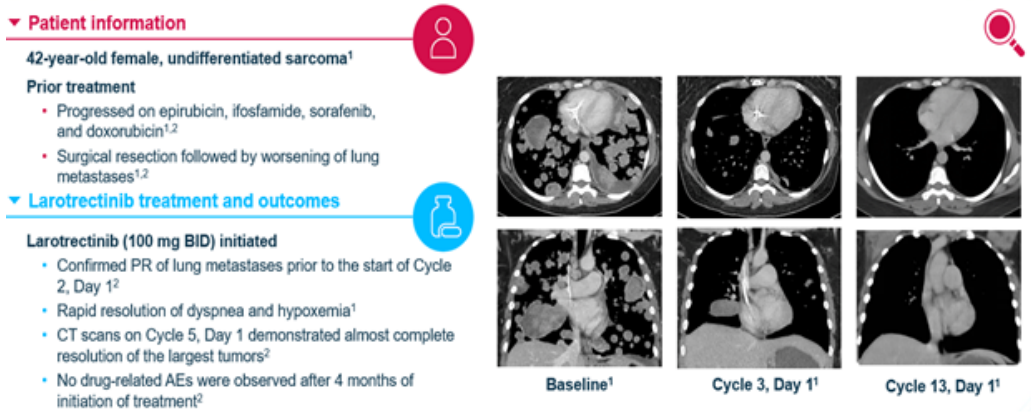 *NB The references in this image do not relate to those at the end of this comment.* A short time to response clearly has patient benefits in terms of symptom relief and quality of life, but also allows for clinicians to evaluate the efficacy and clinical benefit of ongoing medication at an early stage in treatment and discontinue when there is lack of benefit. Whilst appreciating the uncertainty associated with this appraisal, the committee is asked to consider the plausibility of larotrectinib being cost effective to allow for uncertainties to be addressed through use within the CDF. Bayer is not seeking access for larotrectinib through baseline commissioning at this time until uncertainties are addressed. Bayer ask the committee to consider the risk associated with recommending a treatment that is not cost-effective compared to the implications of not recommending a treatment that has the plausibility to be cost-effective and offers benefit to patients who have no other treatment options. Given the innovative nature of this treatment and the relatively low budget impact, the committee is asked to give balanced consideration to downward as well as upward uncertainty that is associated with evaluating this histology independent innovation. Considering the evidence, Bayer believes there is clinical plausibility to the magnitude of benefit modelled and that use within the CDF will allow for further data collection to address uncertainty, whilst enabling patients who currently have no satisfactory treatment options to have the opportunity to gain a response with improved survival and quality of life.	

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			Data collection through the ongoing studies, a global non-interventional study, the EURACAN registry, Genomics England, SACT and Blueteq will allow further information to address uncertainties including: • eligible patient numbers and distribution of tumour types with NTRK gene fusions • prevalence and prognosis of NTRK gene fusion cancer • implementation of the genomic testing service – diagnostic pathway and accuracy • place in therapy and subsequent treatments • progression free survival (PFS) and overall survival (OS) • response in different NTRK tumours **References** (1) Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020. Kummar et al. Patient-Reported Outcomes (PROs) From Two Global Multicenter Clinical Trials of Children and Adults with Tropomyosin Receptor Kinase (TRK) Fusion Cancer Receiving Larotrectinib. Presented at the ASCO annual meeting, May 31 - June 4, 2019, Chicago.	
2	Company	Bayer	The committee concluded that better characterisation of neurotrophic tyrosine receptor kinase (NTRK) gene fusions was needed to fully support the histology-independent approach. A database study in the US has recently reported on the molecular characteristics and prognosis of cancers with NTRK gene fusions (1) .This retrospective study included adult patients with solid malignancies from the de-identified Flatiron Health–Foundation Medicine Clinico-Genomic Database (CGDB; version November 2018) whose tumours had been profiled by comprehensive genomic profiling (CGP) between January 2011 and July 2018. Patients were stratified into two cohorts: patients whose cancer has NTRK gene fusions (Cohort 1) and patients with the same tumour type seen in Cohort 1 but without any known or likely functional NTRK gene alteration (including fusions, loss-of-function mutations, other rearrangements, amplifications, deletions and mutations; Cohort 2). Within each tumour type, matching was conducted between the two cohorts, including factors such as antineoplastic use and ECOG performance status. This study found that the co-occurrence of oncogenic alterations in ALK, BRAF, ERBB2, EGFR, ROS1, and KRAS was uncommon in patients with NTRK gene	Thank you for your comment. During the appraisal, the committee recognised the need for data collection on NTRK characterisation and Bayer's proposal for data collection with Genomics England (see section 3.31 of the FAD)

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			fusions, supporting the hypothesis that NTRK gene fusions are the primary oncogenic drivers in tumours that harbour them. Further work is intended, in collaboration with Genomics England, to characterise NTRK patients in a UK population and inclusion of larotrectinib in the Cancer Drugs Fund (CDF) would allow time for additional data to characterise the NTRK population in the UK to become available. **Reference** (1) Bazhenova et al. Cancers With NTRK Gene Fusions: Molecular Characteristics and Prognosis. Presented at the AACR Precision Medicine meeting, January 9–12, 2020, San Diego, California, United States	
3	Company	Bayer	The committee concluded that further data would be needed to establish whether neurotrophic tyrosine receptor kinase (NTRK) gene fusions affect prognosis. In the database study referred to in 'Comment 2' above, 27 patients from the NTRK fusion cohort were matched with 107 patients in the cohort without any known or likely functional NTRK gene alteration for the overall survival (OS) analysis, and while no clear differences in survival were seen, there was a trend to shorter survival for patients with TRK fusion cancer. Whilst Bayer accept that this is an area of uncertainty, further work is underway to explore the prognostic nature of NTRK gene fusion, including a collaboration with Genomics England.	Thank you for your comment. During the appraisal, the committee recognised the need for data collection on NTRK gene fusion prognosis and Bayer's proposal for data collection with Genomics England (see section 3.31 of the FAD)
4	Company	Bayer	Bayer note that the committee have accepted that Bayer's last line positioning of larotrectinib within the appraisal is appropriate and in line with the marketing authorisation. Patients with advanced cancers have a life-threatening condition and represent an area of unmet medical need. The purpose of treatment in this disease setting is to reduce symptoms of disease, and to prolong survival. In the clinical study programme, for those patients where response to prior systemic therapy was reported, the overall response rate (ORR) to that line of therapy was only [redacted]%; with larotrectinib this figure was 72%. The EPAR for larotrectinib states: ***'the efficacy estimates available today may be considered outstanding in this generally late stage disease setting.'*** (1)	Thank you for your comment. The appraisal committee considered the positioning of larotrectinib (see section 3.5 of the FAD) would be considered as part of ongoing data collection stipulated by the conditional marketing authorisation and further CDF data collection.

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			Of note is the very low event-rate of death recorded in the clinical studies, which was 13.7% (14/102). Bayer note that the committee concluded that larotrectinib's positioning was a major uncertainty and collecting further data would determine how larotrectinib would be used in clinical practice. Entry to the Cancer Drugs Fund (CDF) would allow access to larotrectinib for these patients with no satisfactory treatment options, whilst further data are collected. **Reference** (1) Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020.	
5	Company	Bayer	Bayer note that the committee considered that the pooled analysis of 3 single-arm clinical trials is appropriate for decision making but also raised some concern about generalisability to NHS clinical practice. Neurotrophic tyrosine receptor kinase (NTRK) fusion cancer is a rare disease and not all tumour types have yet been captured in the study programme however, it is important to be aware that patients were recruited sequentially as they presented and no solid tumour type was excluded from the larotrectinib trials. A systematic literature review of NTRK gene fusion identified that the tumour types covered in the trial represent 89% of all those identified in the literature as being associated with NTRK gene fusion. Given that NTRK fusion cancer was not well characterised prior to the development and availability of TRK inhibitors such as larotrectinib, screening for NTRK gene fusions was not widely conducted. As genomic testing becomes more widely adopted across the globe, additional tumour types may be identified where NTRK gene fusions are found. The NAVIGATE and SCOUT studies are still open for enrollment and it is likely that additional tumour types will be identified and studied. Further to this, the overall distribution of tumour types recruited will evolve. Bayer is committed to making these data available should larotrectinib be accepted for use within the Cancer Drugs Fund (CDF), thereby attempting to address this aspect of uncertainty. Further evidence on the distribution of tumour sites will be generated in the real world	Thank you for your comment. During the appraisal, the committee concluded the key evidence was not generalisable to UK clinical practice (see section 3.10 of the FAD). However, it considered further data collection within the CDF could reduce this uncertainty (see section 3.32 of the FAD).

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			setting through the CDF, the non-interventional study and the EURACAN registry.	
6	Company	Bayer	Bayer accept that the overall survival (OS) data are immature; of note is the very low event-rate of death, which was 13.7% (14/102) in the dataset. This results in overall survival extrapolations being subject to uncertainty. Bayer maintain that use within the Cancer Drugs Fund (CDF) will allow for further data collection to address this uncertainty, whilst enabling patients who have no satisfactory treatment options to have the opportunity to gain a rapid and durable response. Bayer acknowledge the points raised about uncertainty of survival projections, but in light of the dramatic responses seen in the context of previous poor responses (se comment 4 above), the OS benefit modelled is indeed plausible. There is recent precedent for impressive survival benefits seen with targeted therapies. Further to this, a wide body of literature reports on early tumour shrinkage (ETS) and extent of tumour shrinkage, 'depth of response' (DepOR), being correlated to survival outcomes. These factors give a plausible biological rationale for the modelled overall survival benefit for larotrectinib when compared to current standard of care for these patients. Further, clinical experts have indicated that a 4-5 fold improvement in survival vs the comparator is clinically plausible. **Literature findings include, in summary:** • A three to four-fold significant increase in OS observed in patients treated with targeted therapies, such as imatinib, when compared to standard of care. Imatinib induced significant increases in OS (3 to 4x) in both chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours (GIST). • Other forms of targeted therapy including trastuzumab for HER2+ breast cancers and various immunotherapy agents also demonstrated significant increases in OS compared to chemotherapy alternatives. • ETS and DepOR serve as indicators of overall response, and correlate with increased progression free survival (PFS), post-progression survival (PPS) and OS across a broad range of tumour types. **Detailed findings** There is evidence in the literature that targeted therapies provide significant increases in OS versus traditional comparators. This suggests the OS benefits modelled for	Thank you for your comment. This evidence for depth of response and early tumour shrinkage were considered at the second appraisal committee meeting. The committee considered that the evidence referred to by the company was for other technologies, including immunotherapies with a different mechanism of action, with no evidence presented for larotrectinib. Therefore, the committee concluded that this concept was possible but speculative given the immaturity of the data (see section 3.22 of the FAD).

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			larotrectinib are clinically plausible and not unprecedented, and this has been confirmed by clinical experts. Imatinib has also transformed the treatment of GIST, where a median OS of 57 months was reported following administration of imatinib in metastatic GIST (1). These results demonstrate a greater than 4-fold increase in OS with imatinib compared to the historical OS of 12–13 months with conventional chemotherapy (2). Moreover, it was deemed unethical to include a non-imatinib comparator arm in the Phase II clinical trial in patients with GIST, and instead, the trial consisted of two arms with different imatinib doses (3)). Use of BCR-ABL1 tyrosine kinase inhibitors (TKIs) which, similar to neurotrophic tyrosine receptor kinase (NTRK) inhibitors, also target a constitutively active tyrosine kinase, have shown significant clinical benefit in patients with CML (4,5). A systematic review of 29 clinical trials revealed an increase in 5-year survival, from 30% to 40% in the pre-imatinib period (1980–87) to 96% after the introduction of the drug (2004–2005) (6), an approximate 3-fold increase in OS. Such was the degree of benefit following imatinib treatment, it was ethically essential to allow crossover from the interferon alpha plus cytarabine arm (7). The increases in OS observed following larotrectinib treatment may be likened to the effect of imatinib in CML and GIST, as not only do the drugs have a similar mechanism of action (both are tyrosine kinase inhibitors), but they also target the driving oncogenic mutation in these cancers (8-10), and thus may behave similarly in terms of improvement in OS. The rapid median time to response to larotrectinib observed (1.8 months) may also be attributed to NTRK being a driver mutation. The significant effects of targeted therapies on OS are also demonstrated with the use of trastuzumab in HER2+ breast cancer. Following its approval in 2000, trastuzumab resulted in an improved 5-year survival from 2% to 31% for patients with HER2+ breast cancer (11). Significant increases in OS are also demonstrated in the era of immunotherapy. Patients with advanced non-small cell lung cancer (NSCLC) treated with atezolizumab, pembrolizumab or nivolumab in combination with a chemotherapeutic agent demonstrated a significant increase in OS compared with chemotherapy alone (12). Treatment with nivolumab plus ipilimumab in patients with advanced melanoma resulted in longer PFS and OS compared to ipilimumab alone (13, 14). Follow-up from the checkmate-017 and checkmate-057 trials showed that nivolumab maintained long-	

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			term OS benefit compared to docetaxel, with 5-year survival rates of 13% vs 3% (15). Of note, the objective response rate (ORR) for nivolumab (20%) or docetaxel (11%) was much lower compared to the ORR observed following treatment with larotrectinib (72%), highlighting that the OS advantage modelled with larotrectinib versus comparators is not unprecedented in solid tumours and suggests it is clinically plausible and reasonable. A further related uncertainty discussed by the committee is the size of the post-progression survival (PPS) benefit. The ACD refers to an 'implausible post-progression survival estimate'. Whilst, Bayer accept that there is uncertainty in the post-progression survival benefit, a significant differential to standard of care is indeed possible as there are several plausible biological mechanisms for this predicted increased survival, and this has been seen in several therapy areas. A review of 10 clinical trials in metastatic colorectal cancer (mCRC) investigating ETS in mCRC demonstrated that ETS differentiates patients with a high sensitivity to treatment. Therefore, ETS is an early indicator of the potentially achievable response and is associated with a more favourable prognosis (16). The same paper also examined DepOR in 3 clinical trials and demonstrated that it can be used as an indicator of the maximum tumour shrinkage observed in a patient and may serve as a predictor of long-term treatment outcome (16). In a later analysis in mCRC, irrespective of treatment, ETS and DepOR were associated with improved PFS, OS and resection rates. Achieving ETS and maximal DepOR are likely to be of particular benefit to patients with symptomatic disease and those with potential to convert to resectable status (17). Moreover, a recently published study in metastatic pancreatic cancer showed that ETS and DepOR were significantly associated with improved PFS and OS. Multivariate analysis confirmed both ETS and DepOR are independently associated with PFS and OS (18). In Cox proportional hazards models, patients with metastatic renal cell carcinoma with ETS had significantly longer OS and PFS compared with patients without ETS (19). A study exploring the association between DepOR to either ALK inhibitors or anti-PD-1 antibodies in NSCLC found that a greater DepOR was not only associated with a longer PFS but also a longer OS (20). Similarly, a study in mCRC found that increased ETS and DepOR in patients treated with chemotherapy and bevacizumab was associated with not only an increased OS and PFS, but also an increased post-progression survival (PPS) (21). There are several other studies in mCRC demonstrating that increased DepOR to targeted therapies predicts prolonged PPS,	

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			meaning that, due to the DepOR whilst on treatment, patients live longer after progression on targeted therapies compared to chemotherapy, usually as a result of a more significant reduction in tumour burden (22, 23). In an analysis by the FDA of DepOR and survival in patients with previously untreated unresectable or metastatic melanoma (UMM), it was found that a larger DepOR correlates with a longer OS, regardless of therapy type. Deep responses were associated with a high rate of estimated OS at 24 months in patients treated with immunotherapy (24). In a further analysis which investigated the prognostic value of DepOR in patients with BRAFV600-mutated metastatic melanoma, greater DepOR was associated with improved survival (25). Notably, larotrectinib not only demonstrates significant ETS with a median time to response of 1.8 months, it also demonstrates significant DepOR for this pre-treated patient group with an ORR of 72%, complete response (CR) (including surgical CR) of 17% and partial response (PR) of 55% (1). In terms of change in tumour size, the median of the maximum percentage decrease from baseline was -66.35% (Range: -100% to 41.2%) and median absolute change was -27.54 mm (Range: -201.7 mm to 25.0 mm) (26). This ETS and DepOR provides a biologically and clinically plausible explanation for the increased PFS, OS and PPS modelled versus comparators for larotrectinib, and that there is precedent in clinical trials in solid tumours for the effects observed. Furthermore, patients on last-line therapies tend to have poorer outcomes. One study demonstrated that receipt of one or more previous lines of chemotherapy resulted in reduced survival time in patients being treated for advanced and recurrent gastric cancer (27). This may explain the differences modelled for patients treated with larotrectinib, considering the dramatic ORR observed, even in patients with ≥3 lines of prior therapy (10). **Validation and conclusions** On this basis, the ICER estimates discussed by the ERG and committee would appear to be implausibly high and Bayer ask that the committee reconsider the preferred assumptions around post-progression survival, particularly in light of the low event rates and the evidence presented above. The modelled survival benefit and the concept of early tumour shrinkage and depth of response being related to survival outcomes was explored with 3 clinical experts ([redacted], [redacted] and [redacted]). All experts agreed that the	

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			larotrectinib efficacy data, together with evidence from the literature regarding other targeted agents, supported the clinical plausibility of the modelled survival benefit. Indeed, based on clinical experience, early response and depth of response can be related to both a progression-free survival and overall survival benefit. **References** 1. Blanke CD et al. J Clin Oncol 2008;26(4):620–625. 2. Antman K et al. J Clin Oncol 1993;11(7):1276–1285. 3. Demetri G et al., N Engl J Med 2002; 347:472-480 4. Vitrakvi® (larotrectinib). Summary of Product Characteristics. October 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf Accessed January 2020. 5. Iqbal N and Iqbal N. Chemotherapy Res Pract 2014;2014:357027. 6. Pulte D et al. Oncologist 2011;16(5):663–671. 7. O'Brien SG et al., N Engl J Med 2003; 348:994-1004 8. Amatu A et al. ESMO Open 2016;1(2):e000023. 9. Jiao X et al. Annals of Oncology 2019;30(5):v25–v54. 10. Hyman DM et al. Poster 445PD; European Society of Medical Oncology. 2019. 11. Sundquist M et al. Breast 2017;31:46–50. 12. Addeo A et al. Front Oncol 2019;9:264. 13. Larkin J et al. N Engl J Med 2015;373(1):23–34. 14. Wolchok JD et al. N Engl J Med 2017;377(14):1345–1356. 15. Gettinger S et al. Journal of Thoracic Oncology 2019;14(10):S244–S245. 16. Heinemann V et al. Eur J Cancer 2015;51(14):1927–1936. 17. Taieb J et al. J Cancer Res and Clin Onc 2018; 144(2):321-335 18. Vivaldi et al. Cancers 2019, 11(7): 939 19. Grunwald V et al. European Urology 2016, 70(6):1006-1015 20. McCoach CE et al. Ann Oncol 2017;28(11):2707–2714. 21. Cremolini C et al. Ann Oncol 2015;26(6):188–1194. 22. Mansmann UR et al. Journal of Clinical Oncology 2017;31(4):427. 23. Somashekhar SP et al. Journal of Clinical Oncology 2019;37(4):631. 24. Osgood C et al. J Clin Oncolo 37, 2019. Abstract #9508 25. Lewis KD et al. British Journal of Cancer 2019. 121:522-528 26. Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020. 27. Kimura M et al. Mol Clin Oncol 2019;10(1):173–179	
7	Company	Bayer	Bayer note that the committee discussed and explored heterogeneity in response to larotrectinib but that they have acknowledged that the trials were not designed to assess heterogeneity in response. The committee have also noted the challenges of	Thank you for your comments. The committee discussed heterogeneity of response further at the second appraisal committee meeting and considered further

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			assessing response because the individual subgroups were too small for meaningful analysis. Whilst there are different overall response rate (ORR) reported by tumour site, the EPAR (1) states: *'With the resulting small samples in most of the cohorts it is difficult to draw conclusions on homogeneity of possible effects between tumour types', and 'these estimates [of ORR] are not robust due to the small sample sizes of individual subgroups.'* Further: *'Due to the small sample size, the confidence intervals are generally wide, making efficacy estimates generally imprecise and hampering the possibility to draw conclusions regarding efficacy in subgroups….'.* The European regulators recognised a certain degree of heterogeneity in response is unavoidable in the same way as there will be important effect modifiers within the scope of any indication, including those based on histology and other patient, disease or treatment characteristics. Further data collection during a period of use within the Cancer Drugs Fund (CDF) will provide additional insight into response rates in tumours identified as being suitable for larotrectinib in clinical practice. **Reference** (1) Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020.	data collection was necessary (see section 3.14 of the FAD).
8	Company	Bayer	Bayer note that the committee considered Bayesian Hierarchical Modelling (BHM) to be a useful way to consider heterogeneity in response to larotrectinib as it was developed specifically for basket trials, and that the output with wide credibility intervals, was more appropriate for decision making because it incorporated some adjustment for heterogeneity. Bayer acknowledge the difficulty of trying to assess potential heterogeneity of response across tumour sites, however Bayer believes that decision making should not be solely based on the BHM outputs as the BHM framework has limitations, due to the assumptions that underpin the analysis. The reduction of the overall response in the ERG's BHM from 72% to 57% was noted by the ERG as '*exploratory and requiring*	Thank you for your comment. The committee noted that the ERG quote refers to exploratory analysis on time-to-event outcomes and not the BHM framework for response data. The committee considered the BHM to be more appropriate because it allowed for some adjustment for heterogeneity of response (see section 3.14 of the FAD)

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			strong assumptions about the link between response and survival outcomes'. Whilst all approaches have limitations, Bayer maintains that the best estimate of overall probability of response is the actual response rate observed. Bayer considers that the ERG's BHM reflects a hypothetical estimate of response and could be considered to represent a 'worst case scenario'.	
9	Company	Bayer	The committee noted that the company did not implement the previous line of therapy analysis appropriately as it considered that a patient's previous unsuccessful line of therapy may not represent best supportive care and that the method was uninformative for overall survival, which was a major uncertainty of the base-case analysis. Of note, the previous line of therapy analysis was not chosen as the company base case and further, Bayer agrees there are other approaches to performing intra-patient comparisons. It is important to note that should the previous line of therapy have not represented best supportive care but rather active treatment, the results of the scenario developed by Bayer are in fact biasing against larotrectinib. Regardless, of this bias against larotrectinib, the results of the different modelling approaches were consistent with the base case ICER.	Thank you for your comment. The committee noted that each indirect comparison likely introduced bias to the analysis (see section 3.17 of the FAD).
10	Company	Bayer	The committee concluded that excluding the possibility of cure in the comparator arm would strongly bias the cost-effectiveness results in favour of larotrectinib and supported why the model structures proposed were not appropriate for a heterogeneous population. Bayer believes that this conclusion is not supported by the evidence. The possibility of cure in the comparator arm is relevant only for a minority of patients with infantile fibrosarcoma (IFS). The bulk of the trial population had advanced or metastatic solid tumours that had progressed despite several prior therapies and it is a requirement of the license that patients have no satisfactory treatment options. Bayer therefore believe that the likelihood of cure in the remainder of the comparator arm is very low. Bayer has conducted analysis which found that removing patients with IFS/ paediatric STS from the model entirely makes minimal difference to the ICER (between -1.6% and +3.2% based on the previous PAS and the post-committee ERG analyses reflecting committee preferences). It is not reasonable to infer that these patients have introduced a strong bias to the analysis.	Thank you for your comment. The committee considered a small number of patients in clinical practice would have tumour types that could potentially be cured because locally advanced and metastatic cancer is generally incurable (see section 3.20 of the FAD). However, the committee considered the population from the trials was not generalisable to clinical practice (see section 3.10 of the FAD) and included many patients that did have potential to be cured without larotrectinib. The committee considered this could strongly bias in favour of larotrectinib. The committee considered the analysis conducted that removes patients with IFS and paediatric STS from the weighted comparator arm in the model to be inappropriate because this does not adjust for the survival benefit in the larotrectinib arm.

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			Bayer believe that the added benefits of limb-sparing, non-mutilating surgery for primary disease post larotrectinib treatment were unaccounted for in the analysis, and that a balanced assessment would also acknowledge that the total benefits of larotrectinib have been underestimated in the analysis. European management of IFS patients may include curative surgery as part of a conservative (organ-sparing) treatment modality, the mainstay of treatment, and surgery should often be considered as completion of a multimodal approach starting with chemotherapy (1, 2). Mutilating surgery should therefore only be proposed after failure of several lines of treatments. Larotrectinib is intended as a treatment option for IFS patients with locally advanced IFS who would require, in the opinion of the Investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection. The majority of IFS patients treated with larotrectinib in the clinical trial program had received one or several previous lines of systemic therapies (mainly vincristine based regimens), in line with a conservative organ-sparing treatment approach. The objective of treating these patients with larotrectinib in the trial was therefore to study its use as part of a conservative treatment approach completed with non-mutilating surgery. In the larotrectinib trial, at the time of data cut-off, a total of 4 of 13 (31%) IFS patients underwent surgery for primary disease after larotrectinib treatment, all of which were limb-sparing, non-mutilating surgery with no anticipated motor/sensory/functional deficit. With more mature follow-up, it is likely this number of patients will increase. Modelling of the benefits of larotrectinib attributable to receiving non-mutilating surgery for primary disease was not possible due to the limited follow-up and small number of patients. Further, making use of the most recent literature sources (1, 2) to inform assumptions about the benefits and costs of a surgical control would have led to increased uncertainty (note that a number of patients in these studies had mutilating surgery with costs attributable to life-long morbidity and amputation). It was not possible to model the benefits of surgery attributable to larotrectinib and it was similarly not possible to model the benefits of surgery post chemotherapy for the control arm, hence the choice of modelling IFS based on STS patients as a proxy where surgery is not a standard treatment option (3). **References** 1. Orbach et al. Infantile Fibrosarcoma: Management Based on the European Experience. Clin Oncol. 2010 28:318-323 2. Orbach et al. Conservative strategy in infantile fibrosarcoma is possible: The European	

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			paediatric Soft tissue sarcoma Study Group experience. European Journal of Cancer 2016. 57; 1e9 3. Mascarenhas et al. Randomized Phase II Window Trial of Two Schedules of Irinotecan With Vincristine in Patients With First Relapse or Progression of Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol. 2010 Oct 20;28(30):4658-63.	
11	Company	Bayer	The committee concluded that the extreme sensitivity of the model output to the survival extrapolations meant that extrapolation did not provide results that the committee could trust. Bayer acknowledge that there is uncertainty around the long-term survival profile for larotrectinib. We also acknowledge that the uncertainty is driven by the immaturity of the data, with ongoing data collection providing more certainty of the outcomes overtime. The base case methodology to explore the survival profile for larotrectinib into the extrapolated period beyond the trial-based Kaplan-Meier follows the DSU preferred fitting of standard parametric curves, resulting in transparent projections for longer term outcomes. The submitted base case curves for progression-free and overall survival are based on statistical goodness of fit and have been validated with clinical experts. The magnitude of the differential of the modelled benefit between larotrectinib and comparator has also been validated in clinical expert interviews Uncertainty around the extrapolated progression-free and overall survival curves applied in the company base case was explored extensively within the submission; including probabilistic sensitivity analysis for the parametric curve parameters using the DSU preferred CHEBS function. Additional scenarios exploring alternative methods for both larotrectinib and comparator survival were performed, including responder/non-responder analysis and application of a naïve Growth Modulation Index to represent a positive hazard ratio for survival profiles of larotrectinib. The underlying challenge is that at the time of the data cut, a large percentage (88/102) of the treated patients were still alive. Extrapolations have been based on a small number of events observed over a short period of time. Uncertainty about the appropriate extrapolation will be reduced once additional events have been observed or if patients continue to experience good long term survival. All current extrapolations predict substantial added benefit. While there is uncertainty around the long-term survival profile for larotrectinib, results of all scenarios show consistently high added benefits for larotrectinib, regardless of methodology and this is supported by the biological plausibility of the survival advantage with larotrectinib, as discussed in comment 6. Importantly, the use of alternative survival functions	Thank you for your comment. The committee considered that data for long-term survival could be collected in the Cancer Drugs Fund.

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			demonstrate both upward and downward uncertainty. Access to larotrectinib in the Cancer Drugs Fund (CDF) would allow time for the survival data to mature and would reduce uncertainty. Bayer contends that a balanced interpretation is that the available data is very encouraging, with high response rates and few deaths and statistical extrapolations suggesting substantial benefit, validated in interviews with clinical experts.	
12	Company	Bayer	The committee considered that there was no plausible reason why post-progression utility would be so much higher for larotrectinib than for the comparator arm for the entire population. Bayer explored the concept of a post-progression utility differential with 3 clinical experts ([redacted], [redacted] and [redacted]) who all agreed that it was indeed clinically plausible that this differential could exist. The experts considered that it made clinical sense to suggest that the quality of life of patients who received larotrectinib and progressed may be better compared with patients who progressed without receiving larotrectinib. This was due to two reasons; 1. the lack of ongoing toxicity from radiotherapy or chemotherapy (e.g. renal impairment, pulmonary fibrosis, neutropenic-driven infections, secondary malignancies and infertility) *There are several potential late effects of anticancer chemotherapy that may affect quality of life including cardiac effects, neurological effects, renal effects, pulmonary effects, impact on fertility as well as secondary malignancies (3).* 2. A greater reduction in tumour burden at the point of progression for patients treated with larotrectinib, due to the significant depth of tumour shrinkage observed in these heavily pre-treated patients, which is not expected with standard of care (i.e. chemotherapy) in this late stage treatment setting *A specific example regarding tumour burden at the point of progression discussed with the experts were patients with head and neck cancer. A high tumour volume can have an impact on eating, drinking, breathing, speaking, as well as resulting in a change in appearance. The significant burden on quality of life was explored with experts, with a reduction in tumour burden expected to*	Thank you for your comment. The committee considered post-progression utility values in section 3.23 of the FAD.

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			improve this. Progressing from a point of reduced tumour burden, could plausibly lead to a differential in post-progression quality of life. There is also precedent in the literature for maintaining a high post-progression utility value, for example in a cost effectiveness analysis of nivolumab vs everolimus in advanced renal cell carcinoma (RCC), the utility values assigned to each health state were as follows: progression free (PF) (complete response/partial response), 0.895; PF (stable disease), 0.846; and progressive disease (PD), 0.817 (1). Another example, again with nivolumab, but this time in carcinoma of the head and neck, used utility values in the cost-effectiveness model of 0.805 for PF and 0.746 for PD (comparator; 0.770 and 0.676 respectively) (2). This is similar to the utilities derived from the larotrectinib study: 0.81 (PF) and 0.74 (PD). The differential in post-progression utility modelled was based on data from the larotrectinib clinical trial programme, and for comparators, from previous NICE TAs or the literature. Whilst Bayer acknowledge that there is limited data from the larotrectinib trial programme, it is clinically plausible that there will be a differential in post-progression utility in favour of larotrectinib and this is borne out by both the literature findings and expert opinion. **References** 1. McCrea C et al. Cost-effectiveness of nivolumab in patients with advanced renal cell carcinoma treated in the United States. Exp Hematol Oncol. 2018;7:4. 2. Haddad R et al. Cost-effectiveness analysis of nivolumab for the treatment of squamous cell carcinoma of the head and neck in the United States. J Med Econ. 2020:1-6 3. Ahmad et al. Anticancer chemotherapy in teenagers and young adults: managing long term side effects. *BMJ* 2016;354:i4567	
13	Company	Bayer	The committee considered that sensitivity analysis to see the effect of equal pre-progression utility values for larotrectinib and the pooled comparator is needed. In the clinical study programme, for those patients where response to prior systemic therapy was reported, the overall response rate (ORR) to that line of therapy was only [redacted]%; with larotrectinib this figure was 72%. As well as high response rates, larotrectinib induced rapid and durable responses, with median time to response of 1.8 months in a population of heavily pre-treated patients, as well as a median of the maximum percentage shrinkage of tumour size of 66% (1). Indeed, the EPAR states '***the efficacy estimates available today may be considered outstanding in this***	Thank you for your comment. The committee considered pre-progression utility values in section 3.24 of the FAD.

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			generally late stage disease setting' (1). Consistent with the early onset of clinical benefits, the degree of tumour shrinkage as well as the favourable safety profile, rapid and sustained clinically meaningful improvements in quality of life were observed with larotrectinib (2). Whilst Bayer acknowledge the limitations of the trial data, studies in the literature indicate that early tumour shrinkage (ETS) and extent of tumour shrinkage (Depth of response 'DepOR') are associated with improvements in quality of life. In a study in metastatic colorectal carcinoma (mCRC), in patients with tumour symptoms at baseline, there were statistically significant improvements in quality of life in those with early tumour shrinkage versus those without early tumour shrinkage. These important data add to the idea that achieving early reductions in tumour load is associated with symptomatic benefit for patients (3) In a study in metastatic breast cancer, for some symptoms, there was a significant association between symptom improvement and objective tumor regression. In these cases, symptom improvement was greatest in those patients who had complete or partial responses, followed by those with stable disease and then those with progressive disease (4). One of the clinical experts Bayer interviewed is a paediatric oncologist, and she discussed a specific example regarding a differential in quality of life whilst on treatment. [redacted] compared the impact on quality of life of chemotherapy and larotrectinib on the child and their family. She specifically mentioned the need for inpatient care with chemotherapy and managing the toxic effects vs outpatient management with oral larotrectinib. The impact is that the child and family can be at home and attend school and work, with the consequent benefits on quality of life. It is therefore clinically plausible that there will be a differential in pre-progression utilities. The low treatment discontinuation rates with larotrectinib (permanent discontinuation due to an AE considered to be treatment-related occurred in [redacted]), compared with rates typically seen with chemotherapy, were also considered in the expert clinician interviews to be illustrative of a potential for a differential in pre-progression utility. An example of a verbatim case study that indicates the significant impact of larotrectinib on quality of life:	

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			"We had a patient with lung cancer who had failed on multiple therapies as his cancer progressed. Within 48 hours of larotrectinib treatment his cough had gone, and he felt he was able to breathe again". **References** (1) Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020. (2) Kummar et al. Patient-Reported Outcomes (PROs) From Two Global Multicenter Clinical Trials of Children and Adults with Tropomyosin Receptor Kinase (TRK) Fusion Cancer Receiving Larotrectinib. Presented at the ASCO annual meeting, May 31 - June 4, 2019, Chicago (3) Siena et al. Quality of life during first-line FOLFOX4±panitumumab in RAS wild-type metastatic colorectal carcinoma: results from a randomized controlled trialESMO Open 2016;1:e000041. (4) Geels et al. Palliative Effect of Chemotherapy: Objective Tumor Response Is Associated With Symptom Improvement in Patients With Metastatic Breast Cancer. J Clin Oncol (2000) 18:2395-2405	
14	Company	Bayer	The committee considered it appropriate to include the 4-week treatment drug wastage scenario in the model. The committee also noted that assumptions relied on using hard capsules which are not yet available, so an additional scenario using the oral solution should have been provided. Bayer considered a scenario whereby only the liquid is used, to have no impact on the base case ICER, due to the flat pricing between the capsules and the liquid form (equal cost per mg). Bayer therefore do not see the relevance of this point as the liquid form will not result in increased wastage compared to capsule form.	Thank you for your comment. The committee consider that drug wastage costs are dependent on administration method and that flat pricing per mg would not change the need for a drug wastage scenario. However, the committee concluded that this issue likely had minimal effect on the cost-effectiveness estimates (see section 3.26 of the FAD).
15	Company	Bayer	The committee concluded that the costs of post-progression larotrectinib should be included but that this issue had not been fully explored. Bayer have previously explored the impact of the cost of larotrectinib treatment post-progression. The average dosage applied in the company submission for adult and paediatric patients includes all administered dosages of larotorectinib, including pre- and post-progression treatment. In the Bayer model, a scenario to the base case was provided whereby the time to treatment discontinuation (TTD) curve was used as an	Thank you for your response. The committee considered that a scenario using time to treatment discontinuation did not fully capture the issue of including costs of post-progression larotrectinib because of the immaturity of the treatment duration data. The committee did not see evidence for how long patients are treated after progression and could not comment on

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			alternative method to model larotrectinib costs. The results of the TTD approach to treatment costing were found to be consistent with the base case when the best fitting (Weibull) curve was applied. Using the exponential TTD curve (the only other plausible model where treatment <1% after 80 years), the ICER decreased.	whether this was appropriate in clinical practice (see section 3.28 of the FAD)
16	Company	Bayer	Bayer are pleased to note that the committee accept that larotrectinib has plausible potential to fulfil the end of life criteria. Bayer also recognise the uncertainty and agree with the committee's observations that use of larotrectinib within the Cancer Drugs Fund (CDF) for these patients who have no satisfactory treatment options would allow for further data collection addressing this uncertainty.	Thank you for your comment. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF.
17	Company	Bayer	Bayer are pleased to note that the committee acknowledge the innovative nature of larotrectinib in (1) representing a major change in the treatment of (neurotrophic tyrosine receptor kinase) NTRK fusion-positive solid tumours, (2) its use in clinical practice would help accelerate NHS England's developments in genomic testing and (3) the improvements in genomic testing would bring wider benefits to the NHS and that these benefits have not been captured in the QALY calculation. Indeed, larotrectinib is a first-in-class, highly selective, histology independent TRK inhibitor. The trial programme tested larotrectinib across a range of adult and paediatric tumour types in which NTRK fusions occur, with patients ranging from one month to 79 years. Efficacy was demonstrated across this diverse group of tumours, all with the common feature of harbouring an NTRK gene fusion, which is an actionable oncogenic driver. Whilst data are immature, the EPAR states: ***'the efficacy estimates available today may be considered outstanding in this generally late stage disease setting.'*** As a result of the early onset of clinical benefits, the degree of tumour shrinkage and the favourable safety profile, rapid and sustained clinically meaningful improvements in quality of life were also observed with larotrectinib. Whilst recognising the considerable challenges and uncertainties associated with this appraisal, the committee is asked to take a pragmatic and balanced approach to uncertainty when weighing up the plausibility of modelling assumptions. Considering the evidence, Bayer believes there is clinical plausibility to the magnitude of benefit we have modelled and that use within the Cancer Drugs Fund (CDF) will	Thank you for your comment. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF.

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			allow for further data collection to address uncertainty.	
18	Commissioner	NHS England	NHS England continues to observe the striking activity of larotrectinib in the population of 102 NTRK gene fusion positive patients reported in the company's submission. The response rate is high, the responses are evident early and the degree of shrinkage of tumour deposits is impressive: the potential benefits of larotrectinib for responding patients with NTRK gene fusions are great. The clinical data however is very immature and hence there are very substantial uncertainties as to both the longer term benefits of larotrectinib and the outcomes of patients once patients progress on larotrectinib.	Thank you for your comment.
19	Commissioner	NHS England	NHS England remains of the view that the correct interpretation of the marketing authorisation is that larotrectinib would be indicated for use once currently commissioned systemic therapies have been used ie for the great majority of patients, larotrectinib would be the 'last line' of systemic therapy. The consequence of this that there would be no further systemic therapies for patients progressing on larotrectinib unless offered within the context of clinical trials.	Thank you for your comment. The committee considered the positioning of larotrectinib (see section 3.5 of the FAD) would be considered as part of ongoing data collection as part of the conditional marketing authorisation.
20	Commissioner	NHS England	<u>Generalisability of the pooled 102 patient data set to clinical practice in England</u> One of the first major issues the Appraisal Committee will have to consider is the generalisability of the company data when translated into clinical practice. NHS England remains concerned that [redacted] of the 93 patients with non-CNS solid tumours in the company submission were treatment naïve to systemic therapy. Of course there are some solid tumours which do not have any commissioned systemic therapy but these are rare. NHS England also notes that salivary gland carcinomas constituted 18% of the 93 patients, infantile fibrosarcoma 14% and thyroid cancer 11%. Thus 43% of the 93 patients were in uncommon/rare tumours that are known to express NTRK gene fusions at a much higher level than the <1% incidence seen in most solid tumours. Whilst such tumours will figure significantly in CDF NHS practice, a national genomic testing service will identify those patients in whom a NTRK gene fusion incidence is very low. Hence NHS England does not expect 43% of CDF entrants for larotrectinib to have these 3 diseases. Soft tissue sarcomas also made up 22% (excluding infantile fibrosarcoma) of the 93 patients, a high proportion when comparing with tumour incidences in England. In addition, 32 of the 102 patients (31%) were aged in the paediatric category. NHS England also notes that there were relatively few patients with the common cancers in the pooled analysis (eg 7 of 93 patients with non-small cell lung cancer, 5 of 93 patients with colorectal cancer). NHS England is content to accept the likelihood of reasonably high response rates in NTRK gene fusion patients in whatever the primary malignancy but is concerned at the contribution in the company's pooled analysis of previously untreated patients, those cancers which express NTRK gene fusions much more frequently than most solid tumours and of paediatric cancers	Thank you for your comment. During the appraisal, the committee concluded the key evidence was not generalisable to UK clinical practice (see section 3.10 of the FAD). However, it considered further data collection within the CDF could reduce this uncertainty (see section 3.32 of the FAD).

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			(especially the very rare infantile fibrosarcoma – see later for incidence figures in England). There is a biologically plausible case that in cancers which are much more frequently driven by NTRK gene fusions (infantile fibrosarcoma, mammary variant salivary gland tumours, secretory breast cancer, congenital mesoblastic nephroma and to a lesser extent thyroid cancer), response rates are higher and benefits greater. The EMA in the larotrectinib EPAR recognised the issue of heterogeneity of response to larotrectinib according to histology and other patient, disease and treatment characteristics. Hong et al have published on 24 February 2020 in Lancet Oncology (https://doi.org/10.1016/S1470-2045(19)30856-3) a pooled analysis of 159 patients with non-CNS solid tumours bearing NTRK gene fusions and treated with larotrectinib. The overall response rate was 79% and larotrectinib was well tolerated. Some details of this 159 patient dataset are similar to the company's 102 patient pooled analysis submitted to NICE: 33% were aged under 18 years (of which almost one half were under 1 year old), 22% had not received any previous systemic therapy and response rates in the <18 year olds was 92% and in adults was 73%. In the Hong report, there were modestly more patients with primary tumours in the lung, colon/rectum, breast and melanoma than in the Bayer submission but still high proportions of infantile fibrosarcoma (18%), other soft tissue sarcomas (26%), thyroid cancer (16%) and salivary gland carcinoma (13%). These latter 4 diseases are highlighted not only because of their high incidences of NTRK gene fusions (infantile fibrosarcoma, thyroid cancer, salivary gland carcinoma) but many of the soft tissue sarcoma cases were in the under 18 year old group (and thus may have higher incidences of NTRK gene fusions than seen in the common cancers). If the 42 patients are selected from the Hong paper with much more obviously adult-type cancers in which NTRK gene fusion incidence is 1% or less, the overall response rate is 55%. If the thyroid and salivary gland cancers are added (total now 89 patients), the response rate rises to 70%. NHS England concludes that in clinical practice in England, the overall response rate is not likely to be as high as 79% but given the contribution of the high incidence NTRK gene fusion cancers, the likely response rate will be above 55%. A figure of between 65% and 70% would seem reasonable. The Cancer Drugs Fund is ideally placed to provide data across the complete spectrum of malignancies but first the company must present the Appraisal Committee with a plausibly cost effective ICER which reflects the above uncertainties as to generalisability from a selected trial population into every day practice in England.	
21	Commissioner	NHS England	<u>Relationship between progression-free, post-progression and overall survival durations</u> Committee D is used to appraising TKIs in non small cell lung cancer (eg the ALK positive TKIs) in which there is evidence of early tumour shrinkage, high response rates and also a high degree of tumour shrinkage ('depth of response'). In clinical trials, patients have scans at	Thank you for your comment. The committee considered survival modelling in sections 3.21-3.22 of the FAD.

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			frequent intervals and as a consequence the RECIST reporting criteria are used to document radiological disease progression which in some patients is not clinically significant as they are asymptomatic. In such circumstances, NICE is used to hearing clinical expert evidence that TKIs are continued until such time that either the patient becomes symptomatic or the rate of disease progression is such that the patient will soon become symptomatic. For ALK inhibitors for example, Committee D has heard evidence from clinicians who indicate that standard practice is to continue TKI therapy post progression for at least several months. NHS England understands that for drugs such as larotrectinib with notable depths of response and after the first detection of progressive disease (ie when patients transition from the progression-free state to the post-progression state in the economic model), the depth of response means that there will be a contribution by larotrectinib to increasing post progression survival when compared with the comparator arm. NHS England notes that Bayer's model assumes that the major incremental survival with larotrectinib occurs in the post progression state. Some of this increment is credible as outlined above but there is no evidence presented by the company to justify this dramatic increase in post progression survival. Many questions remain. Is there evidence that post-progression larotrectinib slows disease progression? Is larotrectinib being continued for prolonged durations post disease progression? Does a greater depth of response translate into a greater duration of larotrectinib post progression? Are 2nd and even 3rd generation TRK inhibitors (which appear on very early data to have significant activity) being used in the larotrectinib trial patients? There are thus clear uncertainties as to post progression survival duration which contribute very significantly to the assessment of cost effectiveness. In its consultation response, Bayer has submitted justification for the phenomena of early tumour shrinkage and the depth of response being correlated to increased progression free survival (PFS), post progression survival and overall survival (OS). It gives published examples in colorectal cancer, non small cell lung cancer, renal cell carcinoma, melanoma and pancreatic cancer. It is common sense that early tumour shrinkage and depth of response would be correlated with PFS duration and thus with whatever relationship PFS then has on extending OS. However, all the examples quoted by the company of depth of response being linked to post progression survival are following 1st line chemotherapy in diseases in which there are commissioned 2nd 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. Given that the use of larotrectinib post progression was common in the trial (in at least one third of patients in the company submission and was also common place in the Hong paper) and as yet there is no data at present to determine the difference between PFS and time to treatment discontinuation, modelling of gains in post progression survival need to be accompanied by different scenarios as to the modelling of different durations of larotrectinib treatment	

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			continuation in the post progression state. NHS England remains circumspect as to the degree of incremental post progression survival in the larotercinib modelling, particularly when it may be biased by those patients with infantile fibrosarcoma and salivary gland carcinoma for example who potentially have surgical options as salvage therapy and constitute a high proportion of patients in the Bayer 102 patient dataset.	
22	Commissioner	NHS England	Utilities NHS England understands that the issue of the utilities used in the different health states in this appraisal is a complicated one, especially with such a wide age range of the treated patients. Both larotrectinib and best supportive care patients should start with the same utility in the progression-free state. However, the high response rates and the low toxicity of larotrectinib will result in a rise in the utility of larotrectinib in the progression free state (but not to a level higher than the utility for a healthy population of the same age range). In the post progression state, it is reasonable for the utility for larotrectinib to initially remain close what it was in the pre-progression state but then to fall as disease progression takes its toll. It is important to state that the comparator for larotrectinib in this analysis is best supportive care and so in the post progression state there should not be any continuing toxicity of chemotherapy affecting the utility value. NHS England would therefore expect the utility values for both arms in the post progression state to equalise once the residual benefit from a good response to larotrectinib has attenuated. How these fluctuating utilities for larotrectinib are managed in terms of values for the pre- and post-progression health states is of course one to be decided by the Appraisal Committee.	Thank you for your comment. The committee considered utility values in sections 3.23-3.24 of the FAD.
23	Commissioner	NHS England	Paediatric malignancy The larotrectinib marketing authorisation is not only solid tumour-agnostic but age-agnostic as well. This means that it is licensed in children of all ages, this being particularly important for patients with infantile fibrosarcoma. The FDA licensed larotrectinib in all ages but restricted the use of entrectinib to patients aged 12 years and older. Entrectinib has not yet received its EMA marketing authorisation and so it is not yet known whether there will be an age restriction. 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. Fibrosarcoma is a very rare malignancy, the PHE 2015 report on rare and less common cancers describing 17 cases of infantile fibrosarcoma in England in the 4 year period of 2010-2013.	Thank you for your comment. The committee recognised the issue of a potential cure in the population of the trials in section 3.20 of the FAD.
24	Commissioner	NHS England	Issues not captured in the ICER If NICE were to recommend larotrectinib to the CDF, this would accelerate the introduction of genomic panel testing in NHS England. This has benefits for current and future patients. There are many current patients who require sequential testing for a variety of genomic changes and who only have small tumour biopsies on which to test: in non small cell lung cancer, for example, tumour biopsies are sequentially tested for EGFR, ALK and ROS1 genomic changes and it is	Thank you for your comment. The committee considered the acceleration of genomic testing in section 3.33 of the FAD.

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			common for there to be insufficient tissue for all of this testing. A genomic panel test would be able to test for all of the actionable genomic changes in one test. Acceleration of genomic panel testing will also benefit future targeted drugs in cancer as it is relatively easy to add the necessary test to an existing panel.	
25	Commissioner	NHS England	[redacted]	Thank you for your comment.
26	Professional group	RCP joint response	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. The appraisal does not fully address the key issue of testing. The test methodology, primary the optimal technology and how this is implemented is key in any overall assessment of cost benefit. As such, in our experts view, NICE needs to additionally consult directly with Genomics England and the Genomic Hubs which come into effect in April 2020 although there is reference to this in 3.7. A molecular biologist with knowledge of fusion biology should be consulted. NICE needs to consider the feasibility and cost of testing as part of the final assessment.	Thank you for your comment. The committee were aware that Genomics England were involved as part of NHS England's response to estimate diagnostic testing costs attributable to this appraisal. The committee considered the feasibility and cost of testing were within NHS England's remit of implementation.
27	Professional group	RCP joint response	We agree with the ERG that the genomic data available are limited and further description of the biology of NTRK fusions and the natural history of associated malignancies, is essential to the continuing discussion.	Thank you for your comment. The committee considered that further data collection of the biology of NTRK gene fusions was necessary within the CDF (see section 3.31 of the FAD)
28	Professional group	RCP joint response	We question the ability of Bayesian and other statistical assessments by the ERG to evaluate the benefit of larotrectinib, and subsequent appraisals for treatment of rare anatomically agnostic molecularly defined cancers. Because of the rarity of these cancers, commonly used and understood assessment methodology may not be suitable to assess benefit and are at risk of dismissing an effective treatment. Clinically there is no doubt that this is an effective treatment.	Thank you for your comment. The committee considered Bayesian Hierarchical modelling was designed for basket trials (see section 3.14 of the FAD), although it recognised substantial uncertainty with the assessment of benefit.
29	Professional group	RCP joint response	Our experts question whether the NICE committee sufficiently constituted to assess molecular therapies in a rare population with difficult testing (cost, logistics and technology)? Our experts noted that they cannot see the constitution of the committee and whether it received advice from a molecular biologist.	Thank you for your comment. The committee were aware that Genomics England were involved as part of NHS England's response to estimate diagnostic testing costs attributable to this appraisal. The committee considered the feasibility and cost of testing were within NHS England's remit of implementation.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
30	Professional group	RCP joint response	Clinicians will be placed in a difficult position. Patients and the general public understand the concept of a targeted drug for a rare mutation and it will be difficult for clinicians to explain why there is no access.	Thank you for your comment. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for larotrectinib. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF.
31	Professional group	RCP joint response	It is essential NICE and other responsible bodies such as Genomics England address their approach, as questioned above, to tumour agnostic molecularly defined therapies as these are fundamentally different to	Thank you for your comment.
32	Patient group	Roy Castle Lung Cancer Foundation	We are disappointed that the Appraisal Committee's preliminary decision is not to recommend Larotrectinib in this indication. This is a new molecular target and it would provide a segmented treatment option for a small, selected group of lung cancer patients.	Thank you for your comment. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for larotrectinib. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF.
33	Patient group	Roy Castle Lung Cancer Foundation	We understand the complexity of this appraisal, both in terms of the provision of testing across tumour sites and also in the immaturity of the data. We would hope that, whilst data matures, giving greater certainty, Larotrectinib would be available to appropriate patients via the Cancer Drugs Fund.	Thank you for your comment. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for larotrectinib. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF.
34	Patient group	GIST Support UK	We are concerned that despite NICE recognising Larotrectinib's potential to meet end of life criteria that it is not being recommended for patients who have no other satisfactory treatment options.	Thank you for your comment. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for larotrectinib. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF.
35	Patient group	GIST Support UK	We are disappointed that the current recommendation prevents patients from accessing this drug because it is not considered to be cost effective use of NHS resources despite recognition that tumours with NTRK gene fusions shrink in response to Larotrectinib. We really hope that Bayer & NICE will negotiate a cost-effective model that will allow access via the CDF to accelerate data collection while treating those patients who have no other targeted treatment options.	
36	Patient group	GIST Support UK	We are pleased that patient comments have been registered in NICE's appraisal (34). We would really like to see NTRK fusion patient's need being addressed in a meaningful way by allowing access to Larotrectinib via the Cancer Drugs Fund and by doing so gather more information.	Thank you for your comment. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for larotrectinib.

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				The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF.
37	Patient group	GIST Support UK	NICE have concluded in the clinical evidence that rare tumour types were over-represented. We understand that the frequency of NTRK fusions is lower in common cancers and higher in rare cancers and while more data needs to be collected do not want to see a situation where those cancer types for whom it has already shown efficacy are denied access.	Thank you for your comment. The committee considered the generalisability of the population in the trials in section 3.10 of the FAD.
38	Patient group	GIST Support UK	We understand that genetic alterations are mutually exclusive, so it is not unreasonable to exclude more common genetic alterations first and then test for NTRK fusions. From a GIST perspective this would match the current pathway. We really hope that for those patients who are then screened for NTRK fusions that those who are found can access Larotrectinib via the CDF.	Thank you for your comment. The committee considered the proposed testing pathway in section 3.7 of the FAD.
39	Patient group	GIST Support UK	NICE recognises the challenge of assessing histology independent treatments such as Larotrectinib within its single technology appraisal process (3.1). Rare cancer patients are naturally low in number and it is harder to collect evidence about the impact of treatment. This conflicts with the NICE process which requires significant amounts of data to make a positive decision. Use of the CDF will provide access to those who need it while gathering the data needed by NICE.	Thank you for your comment. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF whilst further data is collected.
40	Clinical expert	-	These are minor comments but I suggest the following changes to align with the discussion at the meeting regarding sensitivity/specificity of testing, and confirmatory testing: P8: Change “It is available for children’s cancers and sarcomas, although confirmation of the results is needed with DNA-based next generation sequencing (a faster method of sequencing targeted regions of the cancer’s DNA)” To “It is available for children’s cancers and sarcomas, although confirmation of the results is needed with an alternative targeted DNA or RNA test.” P10: Change “Clinical experts considered that DNA and RNA-based next generation sequencing with a confirmatory immunohistochemistry test would be appropriate and minimise the number of false-positive results” to “Clinical experts considered that DNA and RNA-based next generation sequencing with a confirmatory targeted DNA, RNA or immunohistochemistry test in cases in which a positive result is obtained would be appropriate and minimise the number of false-positive results.”	Thank you for your comments. The proposed changes have been included in sections 3.6 and 3.8 of the FAD.
41	Clinical expert	-	I do not feel that the comment “…it is difficult to know how well larotrectinib works because it has not been compared in the trials with other treatments,” is actually possible to address in the current oncology clinical trial framework as we know it (i.e. randomised phase II or III). This type of treatment, being so rarely applied in small subsets of all cancers in practice, would require numerous randomised clinical trials in each cancer type, which will be of inadequate power and few patients would be able to	Thank you for your comment. The committee considered the evidence appropriate for decision making (see section 3.9 of the FAD).

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			enter, over many years- (when it is also highly possible that during the trial the comparator arms / standard of care) changes. As an example, in relatively rare tumours such as cholangiocarcinoma, (one of the cancers in the body of the submitted evidence) - there are only 1500 cases per year in the UK and only around half of these are fit for standard chemotherapy (cisplatin plus gemcitabine) treatment in the first-line setting. Around 1/4 of these patients reach post-first line treatment options, of which 1 in 100 to 1 in 200 patients will have a NTRK-fusion. Thus, this at best would be predictive of less than 5 patients / year in the UK, post-first line to enter a randomised trial. Only half of these would thus get treatment after randomisation. It is difficult to see how this trail will be practical, or to repeat this in say 15-20 different tumour types in parallel.	
42	Clinical expert	-	This is the first NICE appraised cancer therapy as far as I am aware that has changed the paradigm of the way that cancer will be treated in the future and current trial frame works are thus not fit for purpose in an internationally accepted way for testing the NTRK paradigm. Conversely, health economic appraisals and population benefits within the NHS, as well as cost-benefits are likely to need a new framework as this type of treatment will become an increasingly common challenge, akin to modeling in rare diseases.	Thank you for your comment. The committee considered the nature of the appraisal, new analytical frameworks and population benefits to the NHS throughout the appraisal (see sections 3.1, 3.14 and 3.33 of the FAD).
43	Clinical expert	-	Treating NTRK- fusion positive cancers is also highly innovative and groundbreaking and the only other comparison that is currently similarly advanced (ready for clinic) is checkpoint inhibitor therapy (immunotherapy) for MSI-High (microsatellite- high) and/or hyper mutated tumours from any primary cancer site. I.e. like larotrectinib, independent of tumour origin with the same genetic defects. This follows a similar paradigm to NTRK and has already been approved in the some countries, based on single arm, multi-tumour, small patient number, studies.	Thank you for your comment.
44	Clinical expert	-	In my view, CDF and SACT databases (phase IV) are ideal for this type of assessment to assess real population benefits in the UK and I have no current other mechanism to get any higher quality data form what is already published that will be truly comparative - it would be better to do this in an NHS umbrella rather than a company sponsored one, or as a joint programme. This also gives the opportunity of further translational science to allow predicting benefit versus non-benefit genotypes of clinical scenarios.	Thank you for your comment. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF whilst further data is collected, including through the SACT database (see section 3.32 of the FAD).
45	Clinical expert	-	The statement in the ACD “There is little or no evidence about whether larotrectinib works well for every type of NTRK fusion-positive tumour.” Is difficult to comprehend with the evidence discussed and presented. Where it has been tested, the response rates, disease stabilization and waterfall plots are clear where there is high activity in the majority of tumours for a clinically meaningful duration. This type of disease control would not be expected with any conventional agents as most of these patients had no remaining treatment options within known standards of care.	Thank you for your comment. The committee considered that NTRK gene fusion types for which there are no data or limited data would be included in the marketing authorisation and any recommendation (see section 3.10 of the FAD), therefore the committee would need to make the assumption that larotrectinib works well for these tumour types. The committee also noted substantial observed heterogeneity by gene fusion partner (see section 3.13 of the FAD). Therefore, the committee concluded that further data collection within the CDF was necessary (see section 3.32 of the FAD).

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
46	Clinical expert	-	I am concerned that the recommendation biases against children, teenagers and young adults, with incurable advanced neurotrophic tyrosine receptor kinase fusion-positive cancers, especially sarcomas, who have no satisfactory treatment options, and that this treatment might also offer this population major utility in limb preservation. The mental, physical and economic cost of short-term disability, and more so long term, is surely immense.	Thank you for your comment. Following consultation, the company updated their analysis in line with the committee's preferred assumptions as well as an improved value proposition for larotrectinib. The FAD recommends larotrectinib for advanced solid tumours with TRK fusions for use within the CDF.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 6 February 2020 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Bayer plc**

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Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**Current Situation** • Bayer does not have direct or indirect links with, or funding from, manufacturers, distributors or sellers of smoking products but Bayer provides pesticides for crops, which would therefore include tobacco crops. • Bayer is a member of the Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA) (http://www.coresta.org/) within the scope of recommendations of pesticides used for protection of tobacco plants. • It is also a member of country and EU business federations such as the Confederation of British Industry (CBI) and 'Business Europe', which include tobacco companies. **Past Situation** In 2006, Bayer and its subsidiary Icon Genetics piloted a new process for producing biotech drugs in tobacco plants. Icon Genetics was acquired by Nomad Bioscience GmbH from Bayer in 2012.
Name of commentator person completing form:	**Lesley Gilmour**

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1 (Section 1.1)	Bayer are disappointed that larotrectinib for advanced neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours in adults and children who have no satisfactory treatment options has not been recommended for use within the Cancer Drugs Fund (CDF). Bayer recognises the challenges and uncertainties associated with appraising the first histology independent cancer treatment in Europe. Bayer also specifically acknowledge the uncertainty in modelling survival outcomes with immature data when there have been so few deaths in the study programme. Larotrectinib has demonstrated efficacy across a diverse group of tumours and age groups, ranging from one month to 79 years, all with the common feature of harbouring an NTRK gene fusion. As well as high response rates (72%), larotrectinib induced rapid and durable responses, with median time to response of 1.8 months in a population of heavily pre-treated patients, as well as a median of the maximum percentage shrinkage of tumour size of 66% (1). Indeed, the EPAR states '***the efficacy estimates available today may be considered outstanding in this generally late stage disease setting'*** (1). As a result of the early onset of clinical benefits, the degree of tumour shrinkage and the favourable safety profile, rapid and sustained clinically meaningful improvements in quality of life were observed with larotrectinib (2). A case study demonstrating the relationship between speed of response and depth of tumour shrinkage and the corresponding impact on symptoms of the disease is illustrated below

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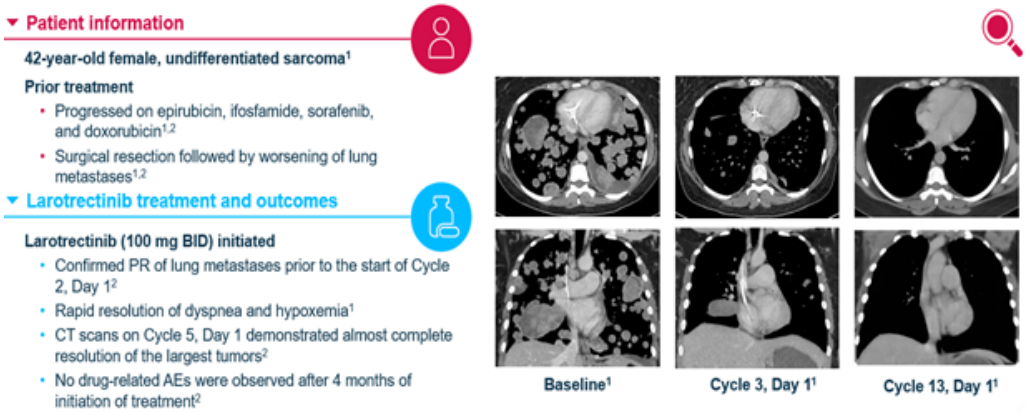

NB The references in this image do not relate to those at the end of this comment.

A short time to response clearly has patient benefits in terms of symptom relief and quality of life, but also allows for clinicians to evaluate the efficacy and clinical benefit of ongoing medication at an early stage in treatment and discontinue when there is lack of benefit.

Whilst appreciating the uncertainty associated with this appraisal, the committee is asked to consider the plausibility of larotrectinib being cost effective to allow for uncertainties to be addressed through use within the CDF. Bayer is not seeking access for larotrectinib through baseline commissioning at this time until uncertainties are addressed. Bayer ask the committee to consider the risk associated with recommending a treatment that is not cost-effective compared to the implications of not recommending a treatment that has the plausibility to be cost-effective and offers benefit to patients who have no other treatment options.

Given the innovative nature of this treatment and the relatively low budget impact, the committee is asked to give balanced consideration to downward as well as upward uncertainty that is associated with evaluating this histology independent innovation.

Considering the evidence, Bayer believes there is clinical plausibility to the magnitude of benefit modelled and that use within the CDF will allow for further data collection to address uncertainty, whilst enabling patients who currently have no satisfactory treatment options to have the opportunity to gain a response with improved survival and quality of life.

Data collection through the ongoing studies, a global non-interventional study, the EURACAN registry, Genomics England, SACT and Blueteq will allow further information to address uncertainties including:

- eligible patient numbers and distribution of tumour types with NTRK gene fusions
- prevalence and prognosis of NTRK gene fusion cancer
- implementation of the genomic testing service – diagnostic pathway and accuracy
- place in therapy and subsequent treatments
- progression free survival (PFS) and overall survival (OS)
- response in different NTRK tumours

References

(1) Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020.

(2) Kummar et al. Patient-Reported Outcomes (PROs) From Two Global Multicenter Clinical Trials of Children and Adults with Tropomyosin Receptor Kinase (TRK) Fusion Cancer Receiving Larotrectinib. Presented at the ASCO annual meeting, May 31 - June 4, 2019, Chicago.

2 (section	The committee concluded that better characterisation of neurotrophic tyrosine receptor kinase

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3.2)	(NTRK) gene fusions was needed to fully support the histology-independent approach. A database study in the US has recently reported on the molecular characteristics and prognosis of cancers with NTRK gene fusions (1) .This retrospective study included adult patients with solid malignancies from the de-identified Flatiron Health–Foundation Medicine Clinico-Genomic Database (CGDB; version November 2018) whose tumours had been profiled by comprehensive genomic profiling (CGP) between January 2011 and July 2018. Patients were stratified into two cohorts: patients whose cancer has NTRK gene fusions (Cohort 1) and patients with the same tumour type seen in Cohort 1 but without any known or likely functional NTRK gene alteration (including fusions, loss-of-function mutations, other rearrangements, amplifications, deletions and mutations; Cohort 2). Within each tumour type, matching was conducted between the two cohorts, including factors such as antineoplastic use and ECOG performance status. This study found that the co-occurrence of oncogenic alterations in ALK, BRAF, ERBB2, EGFR, ROS1, and KRAS was uncommon in patients with NTRK gene fusions, supporting the hypothesis that NTRK gene fusions are the primary oncogenic drivers in tumours that harbour them. Further work is intended, in collaboration with Genomics England, to characterise NTRK patients in a UK population and inclusion of larotrectinib in the Cancer Drugs Fund (CDF) would allow time for additional data to characterise the NTRK population in the UK to become available. **Reference** (1) Bazhenova et al. Cancers With NTRK Gene Fusions: Molecular Characteristics and Prognosis. Presented at the AACR Precision Medicine meeting, January 9–12, 2020, San Diego, California, United States
3 (section 3.3)	The committee concluded that further data would be needed to establish whether neurotrophic tyrosine receptor kinase (NTRK) gene fusions affect prognosis. In the database study referred to in ‘Comment 2’ above, 27 patients from the NTRK fusion cohort were matched with 107 patients in the cohort without any known or likely functional NTRK gene alteration for the overall survival (OS) analysis, and while no clear differences in survival were seen, there was a trend to shorter survival for patients with TRK fusion cancer. Whilst Bayer accept that this is an area of uncertainty, further work is underway to explore the prognostic nature of NTRK gene fusion, including a collaboration with Genomics England.
4 (section 3.5)	Bayer note that the committee have accepted that Bayer’s last line positioning of larotrectinib within the appraisal is appropriate and in line with the marketing authorisation. Patients with advanced cancers have a life-threatening condition and represent an area of unmet medical need. The purpose of treatment in this disease setting is to reduce symptoms of disease, and to prolong survival. In the clinical study programme, for those patients where response to prior systemic therapy was reported, the overall response rate (ORR) to that line of therapy was only ‘academic in confidence information removed’; with larotrectinib this figure was 72%. The EPAR for larotrectinib states: ***‘the efficacy estimates available today may be considered outstanding in this generally late stage disease setting.’*** (1) Of note is the very low event-rate of death recorded in the clinical studies, which was 13.7% (14/102). Bayer note that the committee concluded that larotrectinib’s positioning was a major uncertainty and collecting further data would determine how larotrectinib would be used in clinical practice. Entry to the Cancer Drugs Fund (CDF) would allow access to larotrectinib for these patients with no satisfactory treatment options, whilst further data are collected.

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	Reference (1) Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020.
5 (section 3.9)	Bayer note that the committee considered that the pooled analysis of 3 single-arm clinical trials is appropriate for decision making but also raised some concern about generalisability to NHS clinical practice. Neurotrophic tyrosine receptor kinase (NTRK) fusion cancer is a rare disease and not all tumour types have yet been captured in the study programme however, it is important to be aware that patients were recruited sequentially as they presented and no solid tumour type was excluded from the larotrectinib trials. A systematic literature review of NTRK gene fusion identified that the tumour types covered in the trial represent 89% of all those identified in the literature as being associated with NTRK gene fusion. Given that NTRK fusion cancer was not well characterised prior to the development and availability of TRK inhibitors such as larotrectinib, screening for NTRK gene fusions was not widely conducted. As genomic testing becomes more widely adopted across the globe, additional tumour types may be identified where NTRK gene fusions are found. The NAVIGATE and SCOUT studies are still open for enrollment and it is likely that additional tumour types will be identified and studied. Further to this, the overall distribution of tumour types recruited will evolve. Bayer is committed to making these data available should larotrectinib be accepted for use within the Cancer Drugs Fund (CDF), thereby attempting to address this aspect of uncertainty. Further evidence on the distribution of tumour sites will be generated in the real world setting through the CDF, the non-interventional study and the EURACAN registry.
6 (section 3.11)	Bayer accept that the overall survival (OS) data are immature; of note is the very low event-rate of death, which was 13.7% (14/102) in the dataset. This results in overall survival extrapolations being subject to uncertainty. Bayer maintain that use within the Cancer Drugs Fund (CDF) will allow for further data collection to address this uncertainty, whilst enabling patients who have no satisfactory treatment options to have the opportunity to gain a rapid and durable response. Bayer acknowledge the points raised about uncertainty of survival projections, but in light of the dramatic responses seen in the context of previous poor responses (se comment 4 above), the OS benefit modelled is indeed plausible. There is recent precedent for impressive survival benefits seen with targeted therapies. Further to this, a wide body of literature reports on early tumour shrinkage (ETS) and extent of tumour shrinkage, 'depth of response' (DepOR), being correlated to survival outcomes. These factors give a plausible biological rationale for the modelled overall survival benefit for larotrectinib when compared to current standard of care for these patients. Further, clinical experts have indicated that a 4-5 fold improvement in survival vs the comparator is clinically plausible. **Literature findings include, in summary:** • A three to four-fold significant increase in OS observed in patients treated with targeted therapies, such as imatinib, when compared to standard of care. Imatinib induced significant increases in OS (3 to 4x) in both chronic myeloid leukaemia (CML) and gastrointestinal stromal tumours (GIST). • Other forms of targeted therapy including trastuzumab for HER2+ breast cancers and various

	immunotherapy agents also demonstrated significant increases in OS compared to chemotherapy alternatives. • ETS and DepOR serve as indicators of overall response, and correlate with increased progression free survival (PFS), post-progression survival (PPS) and OS across a broad range of tumour types. **Detailed findings** There is evidence in the literature that targeted therapies provide significant increases in OS versus traditional comparators. This suggests the OS benefits modelled for larotrectinib are clinically plausible and not unprecedented, and this has been confirmed by clinical experts. Imatinib has also transformed the treatment of GIST, where a median OS of 57 months was reported following administration of imatinib in metastatic GIST (1). These results demonstrate a greater than 4-fold increase in OS with imatinib compared to the historical OS of 12–13 months with conventional chemotherapy (2). Moreover, it was deemed unethical to include a non-imatinib comparator arm in the Phase II clinical trial in patients with GIST, and instead, the trial consisted of two arms with different imatinib doses (3)). Use of BCR-ABL1 tyrosine kinase inhibitors (TKIs) which, similar to neurotrophic tyrosine receptor kinase (NTRK) inhibitors, also target a constitutively active tyrosine kinase, have shown significant clinical benefit in patients with CML (4,5). A systematic review of 29 clinical trials revealed an increase in 5-year survival, from 30% to 40% in the pre-imatinib period (1980–87) to 96% after the introduction of the drug (2004–2005) (6), an approximate 3-fold increase in OS. Such was the degree of benefit following imatinib treatment, it was ethically essential to allow crossover from the interferon alpha plus cytarabine arm (7). The increases in OS observed following larotrectinib treatment may be likened to the effect of imatinib in CML and GIST, as not only do the drugs have a similar mechanism of action (both are tyrosine kinase inhibitors), but they also target the driving oncogenic mutation in these cancers (8-10), and thus may behave similarly in terms of improvement in OS. The rapid median time to response to larotrectinib observed (1.8 months) may also be attributed to NTRK being a driver mutation. The significant effects of targeted therapies on OS are also demonstrated with the use of trastuzumab in HER2+ breast cancer. Following its approval in 2000, trastuzumab resulted in an improved 5-year survival from 2% to 31% for patients with HER2+ breast cancer (11). Significant increases in OS are also demonstrated in the era of immunotherapy. Patients with advanced non-small cell lung cancer (NSCLC) treated with atezolizumab, pembrolizumab or nivolumab in combination with a chemotherapeutic agent demonstrated a significant increase in OS compared with chemotherapy alone (12). Treatment with nivolumab plus ipilimumab in patients with advanced melanoma resulted in longer PFS and OS compared to ipilimumab alone (13, 14). Follow-up from the checkmate-017 and checkmate-057 trials showed that nivolumab maintained long-term OS benefit compared to docetaxel, with 5-year survival rates of 13% vs 3% (15). Of note, the objective response rate (ORR) for nivolumab (20%) or docetaxel (11%) was much lower compared to the ORR observed following treatment with larotrectinib (72%), highlighting that the OS advantage modelled with larotrectinib versus comparators is not unprecedented in solid tumours and suggests it is clinically plausible and reasonable. A further related uncertainty discussed by the committee is the size of the post-progression survival (PPS) benefit. The ACD refers to an 'implausible post-progression survival estimate'. Whilst, Bayer accept that there is uncertainty in the post-progression survival benefit, a significant differential to standard of care is indeed possible as there are several plausible biological mechanisms for this predicted increased survival, and this has been seen in several therapy areas.

	A review of 10 clinical trials in metastatic colorectal cancer (mCRC) investigating ETS in mCRC demonstrated that ETS differentiates patients with a high sensitivity to treatment. Therefore, ETS is an early indicator of the potentially achievable response and is associated with a more favourable prognosis (16). The same paper also examined DepOR in 3 clinical trials and demonstrated that it can be used as an indicator of the maximum tumour shrinkage observed in a patient and may serve as a predictor of long-term treatment outcome (16). In a later analysis in mCRC, irrespective of treatment, ETS and DepOR were associated with improved PFS, OS and resection rates. Achieving ETS and maximal DepOR are likely to be of particular benefit to patients with symptomatic disease and those with potential to convert to resectable status (17). Moreover, a recently published study in metastatic pancreatic cancer showed that ETS and DepOR were significantly associated with improved PFS and OS. Multivariate analysis confirmed both ETS and DepOR are independently associated with PFS and OS (18). In Cox proportional hazards models, patients with metastatic renal cell carcinoma with ETS had significantly longer OS and PFS compared with patients without ETS (19). A study exploring the association between DepOR to either ALK inhibitors or anti-PD-1 antibodies in NSCLC found that a greater DepOR was not only associated with a longer PFS but also a longer OS (20). Similarly, a study in mCRC found that increased ETS and DepOR in patients treated with chemotherapy and bevacizumab was associated with not only an increased OS and PFS, but also an increased post-progression survival (PPS) (21). There are several other studies in mCRC demonstrating that increased DepOR to targeted therapies predicts prolonged PPS, meaning that, due to the DepOR whilst on treatment, patients live longer after progression on targeted therapies compared to chemotherapy, usually as a result of a more significant reduction in tumour burden (22, 23). In an analysis by the FDA of DepOR and survival in patients with previously untreated unresectable or metastatic melanoma (UMM), it was found that a larger DepOR correlates with a longer OS, regardless of therapy type. Deep responses were associated with a high rate of estimated OS at 24 months in patients treated with immunotherapy (24). In a further analysis which investigated the prognostic value of DepOR in patients with BRAFV600-mutated metastatic melanoma, greater DepOR was associated with improved survival (25). Notably, larotrectinib not only demonstrates significant ETS with a median time to response of 1.8 months, it also demonstrates significant DepOR for this pre-treated patient group with an ORR of 72%, complete response (CR) (including surgical CR) of 17% and partial response (PR) of 55% (1). In terms of change in tumour size, the median of the maximum percentage decrease from baseline was -66.35% (Range: -100% to 41.2%) and median absolute change was -27.54 mm (Range: -201.7 mm to 25.0 mm) (26). This ETS and DepOR provides a biologically and clinically plausible explanation for the increased PFS, OS and PPS modelled versus comparators for larotrectinib, and that there is precedent in clinical trials in solid tumours for the effects observed. Furthermore, patients on last-line therapies tend to have poorer outcomes. One study demonstrated that receipt of one or more previous lines of chemotherapy resulted in reduced survival time in patients being treated for advanced and recurrent gastric cancer (27). This may explain the differences modelled for patients treated with larotrectinib, considering the dramatic ORR observed, even in patients with ≥3 lines of prior therapy (10). **Validation and conclusions** On this basis, the ICER estimates discussed by the ERG and committee would appear to be implausibly high and Bayer ask that the committee reconsider the preferred assumptions around post-progression survival, particularly in light of the low event rates and the evidence presented above. The modelled survival benefit and the concept of early tumour shrinkage and depth of response being related to survival outcomes was explored with 3 clinical experts 'commercial in confidence

	information removed'. All experts agreed that the larotrectinib efficacy data, together with evidence from the literature regarding other targeted agents, supported the clinical plausibility of the modelled survival benefit. Indeed, based on clinical experience, early response and depth of response can be related to both a progression-free survival and overall survival benefit. **References** 1. Blanke CD et al. J Clin Oncol 2008;26(4):620–625. 2. Antman K et al. J Clin Oncol 1993;11(7):1276–1285. 3. Demetri G et al., N Engl J Med 2002; 347:472-480 4. Vitrakvi® (larotrectinib). Summary of Product Characteristics. October 2019. Available at: https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf Accessed January 2020. 5. Iqbal N and Iqbal N. Chemotherapy Res Pract 2014;2014:357027. 6. Pulte D et al. Oncologist 2011;16(5):663–671. 7. O'Brien SG et al., N Engl J Med 2003; 348:994-1004 8. Amatu A et al. ESMO Open 2016;1(2):e000023. 9. Jiao X et al. Annals of Oncology 2019;30(5):v25–v54. 10. Hyman DM et al. Poster 445PD; European Society of Medical Oncology. 2019. 11. Sundquist M et al. Breast 2017;31:46–50. 12. Addeo A et al. Front Oncol 2019;9:264. 13. Larkin J et al. N Engl J Med 2015;373(1):23–34. 14. Wolchok JD et al. N Engl J Med 2017;377(14):1345–1356. 15. Gettinger S et al. Journal of Thoracic Oncology 2019;14(10):S244–S245. 16. Heinemann V et al. Eur J Cancer 2015;51(14):1927–1936. 17. Taieb J et al. J Cancer Res and Clin Onc 2018; 144(2):321-335 18. Vivaldi et al. Cancers 2019, 11(7): 939 19. Grunwald V et al. European Urology 2016, 70(6):1006-1015 20. McCoach CE et al. Ann Oncol 2017;28(11):2707–2714. 21. Cremolini C et al. Ann Oncol 2015;26(6):188–1194. 22. Mansmann UR et al. Journal of Clinical Oncology 2017;31(4):427. 23. Somashekhar SP et al. Journal of Clinical Oncology 2019;37(4):631. 24. Osgood C et al. J Clin Oncolo 37, 2019. Abstract #9508 25. Lewis KD et al. British Journal of Cancer 2019. 121:522-528 26. Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020. 27. Kimura M et al. Mol Clin Oncol 2019;10(1):173–179
7 (section 3.12)	Bayer note that the committee discussed and explored heterogeneity in response to larotrectinib but that they have acknowledged that the trials were not designed to assess heterogeneity in response. The committee have also noted the challenges of assessing response because the individual subgroups were too small for meaningful analysis. Whilst there are different overall response rate (ORR) reported by tumour site, the EPAR (1) states: *'With the resulting small samples in most of the cohorts it is difficult to draw conclusions on homogeneity of possible effects between tumour types', and 'these estimates [of ORR] are not robust due to the small sample sizes of individual subgroups.'* Further: *'Due to the small sample size, the confidence intervals are generally wide, making efficacy estimates generally imprecise and hampering the possibility to draw conclusions regarding efficacy in subgroups….'.* The European regulators recognised a certain degree of heterogeneity in response is unavoidable in the same way as there will be important effect modifiers within the scope of any indication, including those based on histology and other patient, disease or treatment characteristics. Further data collection during a period of use within the Cancer Drugs Fund (CDF) will provide additional insight into response rates in tumours identified as being suitable for larotrectinib in clinical practice.

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

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	Reference (1) Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020.
8 (section 3.14)	Bayer note that the committee considered Bayesian Hierarchical Modelling (BHM) to be a useful way to consider heterogeneity in response to larotrectinib as it was developed specifically for basket trials, and that the output with wide credibility intervals, was more appropriate for decision making because it incorporated some adjustment for heterogeneity. Bayer acknowledge the difficulty of trying to assess potential heterogeneity of response across tumour sites, however Bayer believes that decision making should not be solely based on the BHM outputs as the BHM framework has limitations, due to the assumptions that underpin the analysis. The reduction of the overall response in the ERG's BHM from 72% to 57% was noted by the ERG as '*exploratory and requiring strong assumptions about the link between response and survival outcomes'*. Whilst all approaches have limitations, Bayer maintains that the best estimate of overall probability of response is the actual response rate observed. Bayer considers that the ERG's BHM reflects a hypothetical estimate of response and could be considered to represent a 'worst case scenario'.
9 (section 3.17)	The committee noted that the company did not implement the previous line of therapy analysis appropriately as it considered that a patient's previous unsuccessful line of therapy may not represent best supportive care and that the method was uninformative for overall survival, which was a major uncertainty of the base-case analysis. Of note, the previous line of therapy analysis was not chosen as the company base case and further, Bayer agrees there are other approaches to performing intra-patient comparisons. It is important to note that should the previous line of therapy have not represented best supportive care but rather active treatment, the results of the scenario developed by Bayer are in fact biasing against larotrectinib. Regardless, of this bias against larotrectinib, the results of the different modelling approaches were consistent with the base case ICER.
10 (section 3.19, 3.20, 3.22)	The committee concluded that excluding the possibility of cure in the comparator arm would strongly bias the cost-effectiveness results in favour of larotrectinib and supported why the model structures proposed were not appropriate for a heterogeneous population. Bayer believes that this conclusion is not supported by the evidence. The possibility of cure in the comparator arm is relevant only for a minority of patients with infantile fibrosarcoma (IFS). The bulk of the trial population had advanced or metastatic solid tumours that had progressed despite several prior therapies and it is a requirement of the license that patients have no satisfactory treatment options. Bayer therefore believe that the likelihood of cure in the remainder of the comparator arm is very low. Bayer has conducted analysis which found that removing patients with IFS/ paediatric STS from the model entirely makes minimal difference to the ICER (between -1.6% and +3.2% based on the previous PAS and the post-committee ERG analyses reflecting committee preferences). It is not reasonable to infer that these patients have introduced a strong bias to the analysis. Bayer believe that the added benefits of limb-sparing, non-mutilating surgery for primary disease post larotrectinib treatment were unaccounted for in the analysis, and that a balanced assessment would also acknowledge that the total benefits of larotrectinib have been underestimated in the analysis.

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	European management of IFS patients may include curative surgery as part of a conservative (organ-sparing) treatment modality, the mainstay of treatment, and surgery should often be considered as completion of a multimodal approach starting with chemotherapy (1, 2). Mutilating surgery should therefore only be proposed after failure of several lines of treatments. Larotrectinib is intended as a treatment option for IFS patients with locally advanced IFS who would require, in the opinion of the Investigator, disfiguring surgery or limb amputation to achieve a complete surgical resection. The majority of IFS patients treated with larotrectinib in the clinical trial program had received one or several previous lines of systemic therapies (mainly vincristine based regimens), in line with a conservative organ-sparing treatment approach. The objective of treating these patients with larotrectinib in the trial was therefore to study its use as part of a conservative treatment approach completed with non-mutilating surgery. In the larotrectinib trial, at the time of data cut-off, a total of 4 of 13 (31%) IFS patients underwent surgery for primary disease after larotrectinib treatment, all of which were limb-sparing, non-mutilating surgery with no anticipated motor/sensory/functional deficit. With more mature follow-up, it is likely this number of patients will increase. Modelling of the benefits of larotrectinib attributable to receiving non-mutilating surgery for primary disease was not possible due to the limited follow-up and small number of patients. Further, making use of the most recent literature sources (1, 2) to inform assumptions about the benefits and costs of a surgical control would have led to increased uncertainty (note that a number of patients in these studies had mutilating surgery with costs attributable to life-long morbidity and amputation). It was not possible to model the benefits of surgery attributable to larotrectinib and it was similarly not possible to model the benefits of surgery post chemotherapy for the control arm, hence the choice of modelling IFS based on STS patients as a proxy where surgery is not a standard treatment option (3). **References** 1. Orbach et al. Infantile Fibrosarcoma: Management Based on the European Experience. Clin Oncol. 2010 28:318-323 2. Orbach et al. Conservative strategy in infantile fibrosarcoma is possible: The European paediatric Soft tissue sarcoma Study Group experience. European Journal of Cancer 2016. 57; 1e9 3. Mascarenhas et al. Randomized Phase II Window Trial of Two Schedules of Irinotecan With Vincristine in Patients With First Relapse or Progression of Rhabdomyosarcoma: A Report From the Children's Oncology Group. J Clin Oncol. 2010 Oct 20;28(30):4658-63.
11 (section 3.20)	The committee concluded that the extreme sensitivity of the model output to the survival extrapolations meant that extrapolation did not provide results that the committee could trust. Bayer acknowledge that there is uncertainty around the long-term survival profile for larotrectinib. We also acknowledge that the uncertainty is driven by the immaturity of the data, with ongoing data collection providing more certainty of the outcomes overtime. The base case methodology to explore the survival profile for larotrectinib into the extrapolated period beyond the trial-based Kaplan-Meier follows the DSU preferred fitting of standard parametric curves, resulting in transparent projections for longer term outcomes. The submitted base case curves for progression-free and overall survival are based on statistical goodness of fit and have been validated with clinical experts. The magnitude of the differential of the modelled benefit between larotrectinib and comparator has also been validated in clinical expert interviews Uncertainty around the extrapolated progression-free and overall survival curves applied in the company base case was explored extensively within the submission; including probabilistic sensitivity analysis for the parametric curve parameters using the DSU preferred CHEBS function. Additional scenarios exploring alternative methods for both larotrectinib and comparator survival were performed, including responder/non-responder analysis and application of a naïve Growth Modulation Index to represent a positive hazard ratio for survival profiles of larotrectinib.

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	The underlying challenge is that at the time of the data cut, a large percentage (88/102) of the treated patients were still alive. Extrapolations have been based on a small number of events observed over a short period of time. Uncertainty about the appropriate extrapolation will be reduced once additional events have been observed or if patients continue to experience good long term survival. All current extrapolations predict substantial added benefit. While there is uncertainty around the long-term survival profile for larotrectinib, results of all scenarios show consistently high added benefits for larotrectinib, regardless of methodology and this is supported by the biological plausibility of the survival advantage with larotrectinib, as discussed in comment 6. Importantly, the use of alternative survival functions demonstrate both upward and downward uncertainty. Access to larotrectinib in the Cancer Drugs Fund (CDF) would allow time for the survival data to mature and would reduce uncertainty. Bayer contends that a balanced interpretation is that the available data is very encouraging, with high response rates and few deaths and statistical extrapolations suggesting substantial benefit, validated in interviews with clinical experts.
12 (section 3.23)	The committee considered that there was no plausible reason why post-progression utility would be so much higher for larotrectinib than for the comparator arm for the entire population. Bayer explored the concept of a post-progression utility differential with 3 clinical experts 'commercial in confidence information removed' who all agreed that it was indeed clinically plausible that this differential could exist. The experts considered that it made clinical sense to suggest that the quality of life of patients who received larotrectinib and progressed may be better compared with patients who progressed without receiving larotrectinib. This was due to two reasons; 1. the lack of ongoing toxicity from radiotherapy or chemotherapy (e.g. renal impairment, pulmonary fibrosis, neutropenic-driven infections, secondary malignancies and infertility) *There are several potential late effects of anticancer chemotherapy that may affect quality of life including cardiac effects, neurological effects, renal effects, pulmonary effects, impact on fertility as well as secondary malignancies (3).* 2. A greater reduction in tumour burden at the point of progression for patients treated with larotrectinib, due to the significant depth of tumour shrinkage observed in these heavily pre-treated patients, which is not expected with standard of care (i.e. chemotherapy) in this late stage treatment setting *A specific example regarding tumour burden at the point of progression discussed with the experts were patients with head and neck cancer. A high tumour volume can have an impact on eating, drinking, breathing, speaking, as well as resulting in a change in appearance. The significant burden on quality of life was explored with experts, with a reduction in tumour burden expected to improve this. Progressing from a point of reduced tumour burden, could plausibly lead to a differential in post-progression quality of life.* There is also precedent in the literature for maintaining a high post-progression utility value, for example in a cost effectiveness analysis of nivolumab vs everolimus in advanced renal cell carcinoma (RCC), the utility values assigned to each health state were as follows: progression free (PF) (complete response/partial response), 0.895; PF (stable disease), 0.846; and progressive disease (PD), 0.817 (1). Another example, again with nivolumab, but this time in carcinoma of the head and neck, used utility values in the cost-effectiveness model of 0.805 for PF and 0.746 for PD (comparator; 0.770 and 0.676 respectively) (2). This is similar to the utilities derived from the larotrectinib study: 0.81 (PF) and 0.74 (PD).

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	The differential in post-progression utility modelled was based on data from the larotrectinib clinical trial programme, and for comparators, from previous NICE TAs or the literature. Whilst Bayer acknowledge that there is limited data from the larotrectinib trial programme, it is clinically plausible that there will be a differential in post-progression utility in favour of larotrectinib and this is borne out by both the literature findings and expert opinion. **References** 1. McCrea C et al. Cost-effectiveness of nivolumab in patients with advanced renal cell carcinoma treated in the United States. Exp Hematol Oncol. 2018;7:4. 2. Haddad R et al. Cost-effectiveness analysis of nivolumab for the treatment of squamous cell carcinoma of the head and neck in the United States. J Med Econ. 2020:1-6 3. Ahmad et al. Anticancer chemotherapy in teenagers and young adults: managing long term side effects. *BMJ* 2016;354:i4567
13 (section 3.26)	The committee considered that sensitivity analysis to see the effect of equal pre-progression utility values for larotrectinib and the pooled comparator is needed. In the clinical study programme, for those patients where response to prior systemic therapy was reported, the overall response rate (ORR) to that line of therapy was only 'academic in confidence information removed'%; with larotrectinib this figure was 72%. As well as high response rates, larotrectinib induced rapid and durable responses, with median time to response of 1.8 months in a population of heavily pre-treated patients, as well as a median of the maximum percentage shrinkage of tumour size of 66% (1). Indeed, the EPAR states '***the efficacy estimates available today may be considered outstanding in this generally late stage disease setting'*** (1). Consistent with the early onset of clinical benefits, the degree of tumour shrinkage as well as the favourable safety profile, rapid and sustained clinically meaningful improvements in quality of life were observed with larotrectinib (2). Whilst Bayer acknowledge the limitations of the trial data, studies in the literature indicate that early tumour shrinkage (ETS) and extent of tumour shrinkage (Depth of response 'DepOR') are associated with improvements in quality of life. In a study in metastatic colorectal carcinoma (mCRC), in patients with tumour symptoms at baseline, there were statistically significant improvements in quality of life in those with early tumour shrinkage versus those without early tumour shrinkage. These important data add to the idea that achieving early reductions in tumour load is associated with symptomatic benefit for patients (3) In a study in metastatic breast cancer, for some symptoms, there was a significant association between symptom improvement and objective tumor regression. In these cases, symptom improvement was greatest in those patients who had complete or partial responses, followed by those with stable disease and then those with progressive disease (4). One of the clinical experts Bayer interviewed is a paediatric oncologist, and she discussed a specific example regarding a differential in quality of life whilst on treatment. 'commercial in confidence information removed' compared the impact on quality of life of chemotherapy and larotrectinib on the child and their family. She specifically mentioned the need for inpatient care with chemotherapy and managing the toxic effects vs outpatient management with oral larotrectinib. The impact is that the child and family can be at home and attend school and work, with the consequent benefits on quality of life. It is therefore clinically plausible that there will be a differential in pre-progression utilities. The low treatment discontinuation rates with larotrectinib (permanent discontinuation due to an AE considered to be treatment-related occurred in 'academic in confidence information removed' compared with rates typically seen with chemotherapy, were also considered in the expert clinician

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	interviews to be illustrative of a potential for a differential in pre-progression utility. An example of a verbatim case study that indicates the significant impact of larotrectinib on quality of life: ***"We had a patient with lung cancer who had failed on multiple therapies as his cancer progressed. Within 48 hours of larotrectinib treatment his cough had gone, and he felt he was able to breathe again".*** **References** (1) Vitrakvi® (larotrectinib). EPAR - Public assessment report. October 2019. Available at: https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf Accessed January 2020. (2) Kummar et al. Patient-Reported Outcomes (PROs) From Two Global Multicenter Clinical Trials of Children and Adults with Tropomyosin Receptor Kinase (TRK) Fusion Cancer Receiving Larotrectinib. Presented at the ASCO annual meeting, May 31 - June 4, 2019, Chicago (3) Siena et al. Quality of life during first-line FOLFOX4±panitumumab in RAS wild-type metastatic colorectal carcinoma: results from a randomized controlled trialESMO Open 2016;1:e000041. (4) Geels et al. Palliative Effect of Chemotherapy: Objective Tumor Response Is Associated With Symptom Improvement in Patients With Metastatic Breast Cancer. J Clin Oncol (2000) 18:2395-2405
14 (section 3.26)	The committee considered it appropriate to include the 4-week treatment drug wastage scenario in the model. The committee also noted that assumptions relied on using hard capsules which are not yet available, so an additional scenario using the oral solution should have been provided. Bayer considered a scenario whereby only the liquid is used, to have no impact on the base case ICER, due to the flat pricing between the capsules and the liquid form (equal cost per mg). Bayer therefore do not see the relevance of this point as the liquid form will not result in increased wastage compared to capsule form.
15 (section 3.28)	The committee concluded that the costs of post-progression larotrectinib should be included but that this issue had not been fully explored. Bayer have previously explored the impact of the cost of larotrectinib treatment post-progression. The average dosage applied in the company submission for adult and paediatric patients includes all administered dosages of larotorectinib, including pre- and post-progression treatment. In the Bayer model, a scenario to the base case was provided whereby the time to treatment discontinuation (TTD) curve was used as an alternative method to model larotrectinib costs. The results of the TTD approach to treatment costing were found to be consistent with the base case when the best fitting (Weibull) curve was applied. Using the exponential TTD curve (the only other plausible model where treatment <1% after 80 years), the ICER decreased.
16 (section 3.29)	Bayer are pleased to note that the committee accept that larotrectinib has plausible potential to fulfil the end of life criteria. Bayer also recognise the uncertainty and agree with the committee's observations that that use of larotrectinib within the Cancer Drugs Fund (CDF) for these patients who have no satisfactory treatment options would allow for further data collection addressing this uncertainty.
17 (section 3.32)	Bayer are pleased to note that the committee acknowledge the innovative nature of larotrectinib in (1) representing a major change in the treatment of (neurotrophic tyrosine receptor kinase) NTRK fusion-positive solid tumours, (2) its use in clinical practice would help accelerate NHS England's

	developments in genomic testing and (3) the improvements in genomic testing would bring wider benefits to the NHS and that these benefits have not been captured in the QALY calculation. Indeed, larotrectinib is a first-in-class, highly selective, histology independent TRK inhibitor. The trial programme tested larotrectinib across a range of adult and paediatric tumour types in which NTRK fusions occur, with patients ranging from one month to 79 years. Efficacy was demonstrated across this diverse group of tumours, all with the common feature of harbouring an NTRK gene fusion, which is an actionable oncogenic driver. Whilst data are immature, the EPAR states: ***'the efficacy estimates available today may be considered outstanding in this generally late stage disease setting.'*** As a result of the early onset of clinical benefits, the degree of tumour shrinkage and the favourable safety profile, rapid and sustained clinically meaningful improvements in quality of life were also observed with larotrectinib. Whilst recognising the considerable challenges and uncertainties associated with this appraisal, the committee is asked to take a pragmatic and balanced approach to uncertainty when weighing up the plausibility of modelling assumptions. Considering the evidence, Bayer believes there is clinical plausibility to the magnitude of benefit we have modelled and that use within the Cancer Drugs Fund (CDF) will allow for further data collection to address uncertainty.

Insert extra rows as needed

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

Revised economic analysis February 2020

Bayer are pleased to submit updated economic analyses based on a revised commercial arrangement for the committee's consideration.

This document sets out the company base case with Bayer's and the committee's preferred assumptions, the ICERs generated by Bayer's alternative modelling approaches, as well as replicating the ERGs model and the additional scenarios requested by the appraisal committee. The analysis with the revised PAS clearly demonstrates that in all cases the ICERs fall below £50,000/QALY (with and without NTRK testing costs), therefore showing a plausible potential to be cost effective at the revised PAS price.

Table 1 List, original PAS and revised PAS (February 2020)

Formulation	List price per pack	Submitted percentage discount	Submitted PAS price per pack	NEW percentage discount (Feb 2020)	NEW PAS price per pack (Feb 2020)
100mg capsules – 56 capsule pack	£14,000	[redacted]	[redacted]	[redacted]	[redacted]
25mg capsules – 56 capsule pack	£3,500	[redacted]	[redacted]	[redacted]	[redacted]
20mg/ml solution – 100ml bottle	£5,000	[redacted]	[redacted]	[redacted]	[redacted]

Table 2 Revised company base case using Bayer's preferred assumptions

Source of results	Larotrectinib	Comparators	Incremental
Treatment cost	[redacted]	[redacted]	[redacted]
Routine care costs	[redacted]	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]	[redacted]
End of life care	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Progression-free life years	[redacted]	[redacted]	[redacted]
Progressed disease life years	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
Progression-free QALYs	[redacted]	[redacted]	[redacted]
Progressed disease QALYs	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER			**£16,155**

Alternative modelling methods: using non-responding patients as a control

This scenario leverages the results from the responder/non-responder stratified survival analysis of patients in the larotrectinib clinical trial programme outlined in Appendix L.1.4 of the original submission.

The full clinical trial cohort, including responders and non-responders to larotrectinib, were applied to the larotrectinib arm while outcomes for non-responders (stable or progressive disease) alone were applied to the comparator arm.

Table 3 Updated company alternative modelling methods: using non-responding patients as a control

Scenario/Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,155
Company submitted responder/non-responder self-control scenario analysis							
Larotrectinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£15,635
Comparator	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: LY; life years, QALYs; quality adjusted life years, ICER; incremental cost-effectiveness ratio

Alternative modelling methods: using previous line of therapy comparison results

The growth modulation index (GMI) compares patient's progression-free survival when treated with larotrectinib versus their time-to-progression on their previous line of therapy. Please refer to Appendix Q of the original submission for details of the methodology.

The analysis compares the average patient's progression-free survival (PFS) when treated with larotrectinib versus the average patient's time-to-treatment progression (TTP) on their prior therapy. This results in a ratio 'the GMI' between 'Period A' (prior therapy) and 'Period B' (larotrectinib) used to assess the comparative effectiveness of larotrectinib versus the prior therapy in delaying disease progression.

Two scenarios were conducted. These reflect the primary GMI analysis and a sensitivity analysis:

- Assessment based on all patients who had received at least 1 prior therapy.
- Assessment of GMI based on those whose previous treatment was in the metastatic disease setting. This additional analysis attempts to control for stage of disease, allowing for a more comparable assessment.

Table 4 Updated company alternative modelling methods: using previous line of therapy comparison results

Scenario/GMI source	GMI value	Larotrectinib			Pooled comparator			
		Costs	QALYs	Life years	Costs	QALYs	Life years	ICER
Base case		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,155
Company submitted previous line of therapy self-control analysis								
All patients who received a prior systemic therapy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£17,006
All patients receiving prior systemic therapy in the metastatic disease setting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£16,217

Abbreviations: GMI; Growth modulation index, QALYs; quality adjusted life years, ICER; incremental cost-effectiveness ratio

Replicated post-committee ERG analyses to reflect committee preferences

These analyses attempt to replicate the results of additional analyses conducted by the ERG and requested by the NICE technical team after the first technology appraisal committee meeting. Bayer were unable to exactly replicate the ICERs presented. The scenarios all apply the following assumptions:

1. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days (in contrast to no administration costs in the company's submission)
2. *Wastage costs assuming patients receive a 28 days' supply of larotrectinib**
3. Post-progression utility independent of treatment ([redacted] for larotrectinib and comparator)
4. Paediatric dose adjustment of larotrectinib (as per ERG base-case)

** Not replicated exactly as methodology unclear (see table below for further explanation)*

The first scenario utilises the company's base case survival approach (larotrectinib PFS and OS extrapolated with Weibull functions, and comparator survival based on a pooled historical comparator). The second scenario utilises the ERG response based survival model with Weibull for PFS and Gompertz for OS extrapolations, and assuming a 57% overall response rate (ORR). Scenarios 3 and 4 apply the ERG response based survival model (as per scenario 2), and further assume that 1) the mean discounted post-progression survival for larotrectinib is the same as for the comparator, and 2) the mean discounted post-progression survival for larotrectinib is the same as the mean discounted overall survival for the comparator, for scenario 3 and 4 respectively.

Table 5 below outlines the replicated post-committee ERG analyses to reflect committee preferences. The table provides an overview of the settings used to achieve the ICERs closest to the scenarios described and summarised in the ACD.

Table 5 Replicated post-committee ERG analyses to reflect committee preferences

Scenario	Model settings	ICER Feb 2020 PAS
Company submitted base case	-	**£16,155**
Scenario 1 (with NTRK testing costs) * *Company's base case survival approach (larotrectinib PFS and OS extrapolated with Weibull functions, and comparator survival based on a pooled historical comparator).*	1. CS partitioned survival model; 2. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days (in contrast to no administration costs in the company's submission); 3. Wastage costs assuming patients receive a 28 days' supply of larotrectinib (not implemented as unclear in report, instead the daily dose for adults set to 175 mg/day; 4. Post-progression utility independent of treatment ([redacted] for larotrectinib and comparator); 5. Paediatric dose adjustment of larotrectinib (as per ERG base-case); 6. Weibull PFS; 7. Weibull OS	**£22,380**
Scenario 1 (without NTRK testing costs)		**£20,775**
Scenario 2 (with NTRK testing costs) * *ERG response based survival model with Weibull for PFS and Gompertz for OS extrapolations, and assuming a 57% overall response rate (ORR).*	1. ERG BHM ERG partitioned response model, ORR=57%; 2. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days (in contrast to no administration costs in the company's submission); 3. Wastage costs assuming patients receive a 28 days' supply of larotrectinib (not implemented as unclear in report, instead the daily dose for adults set to 175 mg/day; 4. Post-progression utility independent of treatment ([redacted] for larotrectinib and comparator); 5. Paediatric dose adjustment of larotrectinib (as per ERG base-case); 6. Weibull PFS; 7. Gompertz OS	**£29,077**
Scenario 2 (without NTRK testing costs)		**£26,466**
Scenario 3 (with NTRK testing costs) * *ERG response based survival model (as per scenario 2), and further assume that the mean discounted post-progression survival for larotrectinib is the same as for the comparator*	1. ERG BHM ERG partitioned response model, ORR=57%; 2. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days (in contrast to no administration costs in the company's submission); 3. Wastage costs assuming patients receive a 28 days' supply of larotrectinib (not implemented as unclear in report, instead the daily dose for adults set to 175 mg/day;	**£45,111**

Scenario	Model settings	ICER Feb 2020 PAS
Company submitted base case	**-**	**£16,155**
Scenario 3 (without NTRK testing costs)	4. Post-progression survival equal for larotrectinib and comparator (response-based survival approach) 5. Paediatric dose adjustment of larotrectinib (as per ERG base-case); 6. Weibull PFS; 7. Gompertz OS	**£40,713**
Scenario 4 (with NTRK testing costs) * *ERG response based survival model (as per scenario 2), and further assume that the mean discounted post-progression survival for larotrectinib is the same as the mean discounted overall survival for the comparator*	1. ERG BHM ERG partitioned response model, ORR=57%; 2. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days (in contrast to no administration costs in the company's submission); 3. Wastage costs assuming patients receive a 28 days' supply of larotrectinib (not implemented as unclear in report, instead the daily dose for adults set to 175 mg/day; 4. Post-progression survival equal to OS for comparator (response-based survival approach) 5. Paediatric dose adjustment of larotrectinib (as per ERG base-case); 6. Weibull PFS; 7. Gompertz OS	**£37,933**
Scenario 4 (without NTRK testing costs)		**£34,328**

Abbreviations: BHM; Bayesian Hierarchal Model, CS; Company submission, ERG; Evidence review Group, GMI; Growth modulation index, NTRK; Neurotrophic Tyrosine Receptor Kinase, NHS; National Health Service, ORR; Overall response rate, OS; Overall survival, PFS; Progression-free survival, QALYs; Quality adjusted life years, ICER; Incremental cost-effectiveness ratio. * Based on ERG's NTRK testing cost estimate by NHS England (average £6,800 per patient treated with larotrectinib)

The analysis clearly indicates that larotrectinib has a plausible potential to be cost effective at the revised PAS price, with all ICERs below £50,000/QALY.

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 6 February 2020 **email:** NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**GIST Support UK**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**We have no past, current, direct or indirect links or funding from the tobacco industry.**
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 6 February 2020 **email:** NICE DOCS

	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**We are concerned that despite NICE recognising Larotrectinib's potential to meet end of life criteria that it is not being recommended for patients who have no other satisfactory treatment options.**
2	**We are disappointed that the current recommendation prevents patients from accessing this drug because it is not considered to be cost effective use of NHS resources despite recognition that tumours with NTRK gene fusions shrink in response to Larotrectinib. We really hope that Bayer & NICE will negotiate a cost-effective model that will allow access via the CDF to accelerate data collection while treating those patients who have no other targeted treatment options.**
3	**We are pleased that patient comments have been registered in NICE's appraisal (34). We would really like to see NTRK fusion patient's need being addressed in a meaningful way by allowing access to Larotrectinib via the Cancer Drugs Fund and by doing so gather more information.**
4	**NICE have concluded in the clinical evidence that rare tumour types were over-represented. We understand that the frequency of NTRK fusions is lower in common cancers and higher in rare cancers and while more data needs to be collected do not want to see a situation where those cancer types for whom it has already shown efficacy are denied access.**
5	**We understand that genetic alterations are mutually exclusive, so it is not unreasonable to exclude more common genetic alterations first and then test for NTRK fusions. From a GIST perspective this would match the current pathway. We really hope that for those patients who are then screened for NTRK fusions that those who are found can access Larotrectinib via the CDF.**
6	**NICE recognises the challenge of assessing histology independent treatments such as Larotrectinib within its single technology appraisal process (3.1). Rare cancer patients are naturally low in number and it is harder to collect evidence about the impact of treatment. This conflicts with the NICE process which requires significant amounts of data to make a positive decision. Use of the CDF will provide access to those who need it while gathering the data needed by NICE.**

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must

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send it by the deadline.

- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Response to the National Institute for Health and Care Excellence's Appraisal Consultation Document (ACD) on Larotrectinib for treating advanced, NTRK fusion positive solid tumours. [ID 1299]

This response is submitted by Roy Castle Lung Cancer Foundation.

- We are disappointed that the Appraisal Committee's preliminary decision is not to recommend Larotrectinib in this indication. This is a new molecular target and it would provide a segmented treatment option for a small, selected group of lung cancer patients.

- We understand the complexity of this appraisal, both in terms of the provision of testing across tumour sites and also in the immaturity of the data. We would hope that, whilst data matures, giving greater certainty, Larotrectinib would be available to appropriate patients via the Cancer Drugs Fund.

Roy Castle Lung Cancer Foundation
February 2020

NICE National Institute for Health and Care Excellence

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

Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 6 February 2020 **email:** NICE DOCS

	The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced.
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NCRI-ACP-RCP-RCR
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

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

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with our experts and would like to make the following comments. The appraisal does not fully address the key issue of testing. The test methodology, primary the optimal technology and how this is implemented is key in any overall assessment of cost benefit. As such, in our experts view, NICE needs to additionally consult directly with Genomics England and the Genomic Hubs which come into effect in April 2020 although there is reference to this in 3.7. A molecular biologist with knowledge of fusion biology should be consulted. NICE needs to consider the feasibility and cost of testing as part of the final assessment.
2	We agree with the ERG that the genomic data available are limited and further description of the biology of NTRK fusions and the natural history of associated malignancies, is essential to the continuing discussion.
3	We question the ability of Bayesian and other statistical assessments by the ERG to evaluate the benefit of larotrectinib, and subsequent appraisals for treatment of rare anatomically agnostic molecularly defined cancers. Because of the rarity of these cancers, commonly used and understood assessment methodology may not be suitable to assess benefit and are at risk of dismissing an effective treatment. Clinically there is no doubt that this is an effective treatment.
4	Our experts question whether the NICE committee sufficiently constituted to assess molecular therapies in a rare population with difficult testing (cost, logistics and technology)? Our experts noted that they cannot see the constitution of the committee and whether it received advice from a molecular biologist.
5	Clinicians will be placed in a difficult position. Patients and the general public understand the concept of a targeted drug for a rare mutation and it will be difficult for clinicians to explain why there is no access.
6	It is essential NICE and other responsible bodies such as Genomics England address their approach, as questioned above, to tumour agnostic molecularly defined therapies as these are fundamentally different to

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NHS England submission on the NICE consultation on the appraisal of larotrectinib for the treatment of NTRK gene fusion positive patients with solid tumours which are locally advanced or metastatic or which would require a resection likely to result in severe morbidity AND for whom there are no satisfactory treatment options for their disease

This submission contains redacted information which is commercial in confidence.

1. NHS England continues to observe the striking activity of larotrectinib in the population of 102 NTRK gene fusion positive patients reported in the company's submission. The response rate is high, the responses are evident early and the degree of shrinkage of tumour deposits is impressive: the potential benefits of larotrectinib for responding patients with NTRK gene fusions are great. The clinical data however is very immature and hence there are very substantial uncertainties as to both the longer term benefits of larotrectinib and the outcomes of patients once patients progress on larotrectinib.
2. NHS England remains of the view that the correct interpretation of the marketing authorisation is that larotrectinib would be indicated for use once currently commissioned systemic therapies have been used ie for the great majority of patients, larotrectinib would be the 'last line' of systemic therapy. The consequence of this that there would be no further systemic therapies for patients progressing on larotrectinib unless offered within the context of clinical trials.

Generalisability of the pooled 102 patient data set to clinical practice in England

3. One of the first major issues the Appraisal Committee will have to consider is the generalisability of the company data when translated into clinical practice. NHS England remains concerned that [redacted] of the 93 patients with non-CNS solid tumours in the company submission were treatment naïve to systemic therapy. Of course there are some solid tumours which do not have any commissioned systemic therapy but these are rare.
4. NHS England also notes that salivary gland carcinomas constituted 18% of the 93 patients, infantile fibrosarcoma 14% and thyroid cancer 11%. Thus 43% of the 93 patients were in uncommon/rare tumours that are known to express NTRK gene fusions at a much higher level than the <1% incidence seen in most solid tumours. Whilst such tumours will figure significantly in CDF NHS practice, a national genomic testing service will identify those patients in whom a NTRK gene fusion incidence is very low. Hence NHS England does not expect 43% of CDF entrants for larotrectinib to have these 3 diseases.
5. Soft tissue sarcomas also made up 22% (excluding infantile fibrosarcoma) of the 93 patients, a high proportion when comparing with tumour incidences in England. In addition, 32 of the 102 patients (31%) were aged in the paediatric category.

6. NHS England also notes that there were relatively few patients with the common cancers in the pooled analysis (eg 7 of 93 patients with non-small cell lung cancer, 5 of 93 patients with colorectal cancer).
7. NHS England is content to accept the likelihood of reasonably high response rates in NTRK gene fusion patients in whatever the primary malignancy but is concerned at the contribution in the company's pooled analysis of previously untreated patients, those cancers which express NTRK gene fusions much more frequently than most solid tumours and of paediatric cancers (especially the very rare infantile fibrosarcoma – see later for incidence figures in England). There is a biologically plausible case that in cancers which are much more frequently driven by NTRK gene fusions (infantile fibrosarcoma, mammary variant salivary gland tumours, secretory breast cancer, congenital mesoblastic nephroma and to a lesser extent thyroid cancer), response rates are higher and benefits greater. The EMA in the larotrectinib EPAR recognised the issue of heterogeneity of response to larotrectinib according to histology and other patient, disease and treatment characteristics.
8. Hong et al have published on 24 February 2020 in Lancet Oncology (https://doi.org/10.1016/S1470-2045(19)30856-3) a pooled analysis of 159 patients with non-CNS solid tumours bearing NTRK gene fusions and treated with larotrectinib. The overall response rate was 79% and larotrectinib was well tolerated.
9. Some details of this 159 patient dataset are similar to the company's 102 patient pooled analysis submitted to NICE: 33% were aged under 18 years (of which almost one half were under 1 year old), 22% had not received any previous systemic therapy and response rates in the <18 year olds was 92% and in adults was 73%.
10. In the Hong report, there were modestly more patients with primary tumours in the lung, colon/rectum, breast and melanoma than in the Bayer submission but still high proportions of infantile fibrosarcoma (18%), other soft tissue sarcomas (26%), thyroid cancer (16%) and salivary gland carcinoma (13%). These latter 4 diseases are highlighted not only because of their high incidences of NTRK gene fusions (infantile fibrosarcoma, thyroid cancer, salivary gland carcinoma) but many of the soft tissue sarcoma cases were in the under 18 year old group (and thus may have higher incidences of NTRK gene fusions than seen in the common cancers). If the 42 patients are selected from the Hong paper with much more obviously adult-type cancers in which NTRK gene fusion incidence is 1% or less, the overall response rate is 55%. If the thyroid and salivary gland cancers are added (total now 89 patients), the response rate rises to 70%.
11. NHS England concludes that in clinical practice in England, the overall response rate is not likely to be as high as 79% but given the contribution of the high incidence NTRK gene fusion cancers, the likely response rate will be above 55%. A figure of between 65% and 70% would seem reasonable.
12. The Cancer Drugs Fund is ideally placed to provide data across the complete spectrum of malignancies but first the company must present the Appraisal

Committee with a plausibly cost effective ICER which reflects the above uncertainties as to generalisability from a selected trial population into every day practice in England.

Relationship between progression-free, post-progression and overall survival durations

13. Committee D is used to appraising TKIs in non small cell lung cancer (eg the ALK positive TKIs) in which there is evidence of early tumour shrinkage, high response rates and also a high degree of tumour shrinkage ('depth of response'). In clinical trials, patients have scans at frequent intervals and as a consequence the RECIST reporting criteria are used to document radiological disease progression which in some patients is not clinically significant as they are asymptomatic. In such circumstances, NICE is used to hearing clinical expert evidence that TKIs are continued until such time that either the patient becomes symptomatic or the rate of disease progression is such that the patient will soon become symptomatic. For ALK inhibitors for example, Committee D has heard evidence from clinicians who indicate that standard practice is to continue TKI therapy post progression for at least several months.
14. NHS England understands that for drugs such as larotrectinib with notable depths of response and after the first detection of progressive disease (ie when patients transition from the progression-free state to the post-progression state in the economic model), the depth of response means that there will be a contribution by larotrectinib to increasing post progression survival when compared with the comparator arm.
15. NHS England notes that Bayer's model assumes that the major incremental survival with larotrectinib occurs in the post progression state. Some of this increment is credible as outlined above but there is no evidence presented by the company to justify this dramatic increase in post progression survival. Many questions remain. Is there evidence that post-progression larotrectinib slows disease progression? Is larotrectinib being continued for prolonged durations post disease progression? Does a greater depth of response translate into a greater duration of larotrectinib post progression? Are 2nd and even 3rd generation TRK inhibitors (which appear on very early data to have significant activity) being used in the larotrectinib trial patients? There are thus clear uncertainties as to post progression survival duration which contribute very significantly to the assessment of cost effectiveness.
16. In its consultation response, Bayer has submitted justification for the phenomena of early tumour shrinkage and the depth of response being correlated to increased progression free survival (PFS), post progression survival and overall survival (OS). It gives published examples in colorectal cancer, non small cell lung cancer, renal cell carcinoma, melanoma and pancreatic cancer. It is common sense that early tumour shrinkage and depth of response would be correlated with PFS duration and thus with whatever relationship PFS then has on extending OS. However, all the examples

quoted by the company of depth of response being linked to post progression survival are following 1st line chemotherapy in diseases in which there are commissioned 2nd 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.

17. Given that the use of larotrectinib post progression was common in the trial (in at least one third of patients in the company submission and was also common place in the Hong paper) and as yet there is no data at present to determine the difference between PFS and time to treatment discontinuation, modelling of gains in post progression survival need to be accompanied by different scenarios as to the modelling of different durations of larotrectinib treatment continuation in the post progression state.
18. NHS England remains circumspect as to the degree of incremental post progression survival in the laroterctinib modelling, particularly when it may be biased by those patients with infantile fibrosarcoma and salivary gland carcinoma for example who potentially have surgical options as salvage therapy and constitute a high proportion of patients in the Bayer 102 patient dataset.

<u>Utilities</u>

19. NHS England understands that the issue of the utilities used in the different health states in this appraisal is a complicated one, especially with such a wide age range of the treated patients. Both larotrectinib and best supportive care patients should start with the same utility in the progression-free state. However, the high response rates and the low toxicity of larotrectinib will result in a rise in the utility of larotrectinib in the progression free state (but not to a level higher than the utility for a healthy population of the same age range). In the post progression state, it is reasonable for the utility for larotrectinib to initially remain close what it was in the pre-progression state but then to fall as disease progression takes its toll. It is important to state that the comparator for larotrectinib in this analysis is best supportive care and so in the post progression state there should not be any continuing toxicity of chemotherapy affecting the utility value. NHS England would therefore expect the utility values for both arms in the post progression state to equalise once the residual benefit from a good response to larotrectinib has attenuated.
20. How these fluctuating utilities for larotrectinib are managed in terms of values for the pre- and post-progression health states is of course one to be decided by the Appraisal Committee.

Paediatric malignancy

21. The larotrectinib marketing authorisation is not only solid tumour-agnostic but age-agnostic as well. This means that it is licensed in children of all ages, this being particularly important for patients with infantile fibrosarcoma. The FDA licensed larotrectinib in all ages but restricted the use of entrectinib to patients aged 12 years and older [redacted]
22. 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. Fibrosarcoma is a very rare malignancy, the PHE 2015 report on rare and less common cancers describing 17 cases of infantile fibrosarcoma in England in the 4 year period of 2010-2013.

Issues not captured in the ICER

23. If NICE were to recommend larotrectinib to the CDF, this would accelerate the introduction of genomic panel testing in NHS England. This has benefits for current and future patients. There are many current patients who require sequential testing for a variety of genomic changes and who only have small tumour biopsies on which to test: in non small cell lung cancer, for example, tumour biopsies are sequentially tested for EGFR, ALK and ROS1 genomic changes and it is common for there to be insufficient tissue for all of this testing. A genomic panel test would be able to test for all of the actionable genomic changes in one test. Acceleration of genomic panel testing will also benefit future targeted drugs in cancer as it is relatively easy to add the necessary test to an existing panel.

[redacted]

[redacted]

Prof Peter Clark

National Clinical lead for the Cancer Drugs Fund

NHS England

February 2020

NICE National Institute for Health and Care Excellence

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Consultation on the appraisal consultation document – deadline for comments 5pm on Thursday 6 February 2020 **email:** NICE DOCS

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Insert organisation name**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**Insert disclosure here**]
Name of commentator person completing form:	Alistair Reid

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.

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NICE National Institute for Health and Care Excellence

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

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1	These are minor comments but I suggest the following changes to align with the discussion at the meeting regarding sensitivity/specificity of testing, and confirmatory testing: P8: Change "It is available for children's cancers and sarcomas, although confirmation of the results is needed with DNA-based next generation sequencing (a faster method of sequencing targeted regions of the cancer's DNA)" To "It is available for children's cancers and sarcomas, although confirmation of the results is needed with an alternative targeted DNA or RNA test." P10: Change "Clinical experts considered that DNA and RNA-based next generation sequencing with a confirmatory immunohistochemistry test would be appropriate and minimise the number of false-positive results" to "Clinical experts considered that DNA and RNA-based next generation sequencing with a confirmatory targeted DNA, RNA or immunohistochemistry test in cases in which a positive result is obtained would be appropriate and minimise the number of false-positive results."

Checklist for submitting comments

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- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
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Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Company nominated external medical expert
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[**Harpreet Singh Wasan**]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	I do not feel that the comment **"…it is difficult to know how well larotrectinib works because it has not been compared in the trials with other treatments,"** is actually possible to address in the current oncology clinical trial framework as we know it (i.e. randomised phase II or III). This type of treatment, being so rarely applied in small subsets of all cancers in practice, would require numerous randomised clinical trials in each cancer type, which will be of inadequate power and few patients would be able to enter, over many years- (when it is also highly possible that during the trial the comparator arms / standard of care) changes. As an example, in relatively rare tumours such as cholangiocarcinoma, (one of the cancers in the body of the submitted evidence) - there are only 1500 cases per year in the UK and only around half of these are fit for standard chemotherapy (cisplatin plus gemcitabine) treatment in the first-line setting. Around 1/4 of these patients reach post-first line treatment options, of which 1 in 100 to 1 in 200 patients will have a NTRK-fusion. Thus, this at best would be predictive of less than 5 patients / year in the UK, post-first line to enter a randomised trial. Only half of these would thus get treatment after randomisation. It is difficult to see how this trail will be practical, or to repeat this in say 15-20 different tumour types in parallel.
2	This is the first NICE appraised cancer therapy as far as I am aware that has changed the paradigm of the way that cancer will be treated in the future and current trial frame works are thus not fit for purpose in an internationally accepted way for testing the NTRK paradigm. Conversely, health economic appraisals and population benefits within the NHS, as well as cost-benefits are likely to need a new framework as this type of treatment will become an increasingly common challenge, akin to modeling in rare diseases.
3	Treating NTRK- fusion positive cancers is also highly innovative and groundbreaking and the only other comparison that is currently similarly advanced (ready for clinic) is checkpoint inhibitor therapy (immunotherapy) for MSI-High (microsatellite- high) and/or hyper mutated tumours from any primary cancer site. I.e. like larotrectinib,

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	independent of tumour origin with the same genetic defects. This follows a similar paradigm to NTRK and has already been approved in the some countries, based on single arm, multi-tumour, small patient number, studies.
4	In my view, CDF and SACT databases (phase IV) are ideal for this type of assessment to assess real population benefits in the UK and I have no current other mechanism to get any higher quality data form what is already published that will be truly comparative - it would be better to do this in an NHS umbrella rather than a company sponsored one, or as a joint programme. This also gives the opportunity of further translational science to allow predicting benefit versus non-benefit genotypes of clinical scenarios.
5	The statement in the ACD "There is little or no evidence about whether larotrectinib works well for every type of NTRK fusion-positive tumour." Is difficult to comprehend with the evidence discussed and presented. Where it has been tested, the response rates, disease stabilization and waterfall plots are clear where there is high activity in the majority of tumours for a clinically meaningful duration. This type of disease control would not be expected with any conventional agents as most of these patients had no remaining treatment options within known standards of care.
6	I am concerned that the recommendation biases against children, teenagers and young adults, with incurable advanced neurotrophic tyrosine receptor kinase fusion-positive cancers, especially sarcomas, who have no satisfactory treatment options, and that this treatment might also offer this population major utility in limb preservation. The mental, physical and economic cost of short-term disability, and more so long term, is surely immense.

Insert extra rows as needed

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Larotrectinib for treating NTRK fusion-positive advanced solid tumours

Evidence review group's comment on company's February 2020 revised analysis

Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

In February 2020 the company submitted an updated economic analysis based on a revised patient access scheme (PAS). The PAS consisted of a simple discount of [redacted] over the list price of larotrectinib (see Table 1 of company's updated analysis). The analysis updated the results of the following analyses with the most recent PAS price:

1. Company's base-case
2. Company's scenarios considering two alternative methods to model PFS and OS for the comparator
   2.1. Using non-responding patients as control
   2.2. Using patients on a previous line of treatment as control
3. ERG's additional analyses conducted after the first committee meeting and incorporating the committees preferred assumptions.

The ERG attempted to replicate the results of the analyses described in 1 and 3. The results of the analysis described in 2.1. were not validated by the ERG, because this modelling approach is already considered within the analyses described in 3. We also did not validate the results of the analysis described in 2.2 because the implementation of this modelling approach had been considered methodologically flawed (see Appraisal Consultation Document).

The company presented the results of their revised base-case in Table 2 of the updated analysis. The ERG was able to replicate all presented results after updating the unit cost of larotrectinib to reflect the latest PAS.

However, we could not replicate the results for the updated ERG's additional analyses reported in Table 5 of the company's updated analysis. In this set of analyses, the company's claims to have incorporate the following assumptions:

1. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days
2. Wastage costs assuming patients receive a 28 days' supply of larotrectinib
3. Post-progression utility independent of treatment ([redacted] for larotrectinib and comparator)
4. Paediatric dose adjustment of larotrectinib (as per ERG base-case)

The company further states that they did not replicate the ERG's methodology to implement the wastage assumption, as this was unclear. Instead they claim to have applied an alternative daily dose of larotrectinib ([redacted] mg/day) for adults. The ERG notes that this is a reduction in the adult daily dose

compared to what had been used throughout the appraisal by both the company and ERG ([redacted] mg/day), so it is unclear to the ERG how this approach is supposed to reflect wastage for a 28 days prescribing pattern as opposed to a weekly one (company's base case). The ERG did not obtain the same ICERs when setting the model with a [redacted]mg/day dose of larotrectinib and a once a week prescribing pattern. These results are not shown, as this implementation of the 28 days wastage assumption was not considered correct.

The ERG run the analyses described in Table 5 the company's updated analysis and setting the prescribing pattern of larotrectinib to 28 days (a functionality implemented by the company in the model submitted with their response to clarification questions). Table 5 in the company's updated analysis is reported below with an additional column for the ICERs as estimated by the ERG (see Table 1).

Table 1 Company's Table 5 updated with ICERs estimated by the ERG

Scenario	Model settings	ICER Feb 2020 PAS (per QALY)	ICER Feb 2020 PAS ERG** (per QALY)
Company submitted base case	-	**£16,155**	
Scenario 1 (with NTRK testing costs) * *Company's base case survival approach (larotrectinib PFS and OS extrapolated with Weibull functions, and comparator survival based on a pooled historical comparator).*	1. CS partitioned survival model; 2. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days (in contrast to no administration costs in the company's submission); 3. Wastage costs assuming patients receive a 28 days' supply of larotrectinib (not implemented as unclear in report, instead the daily dose for adults set to [redacted] mg/day; 4. Post-progression utility independent of treatment ([redacted] for larotrectinib and comparator); 5. Paediatric dose adjustment of larotrectinib (as per ERG base-case); 6. Weibull PFS; 7. Weibull OS	**£22,380**	**£23,639**
Scenario 1 (without NTRK testing costs)		**£20,775**	**£22,034**
Scenario 2 (with NTRK testing costs) * *ERG response based survival model with Weibull for PFS and Gompertz for OS extrapolations, and assuming a 57% overall response rate (ORR).*	1. ERG BHM ERG partitioned response model, ORR=57%; 2. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days (in contrast to no administration costs in the company's submission); 3. Wastage costs assuming patients receive a 28 days' supply of larotrectinib (not implemented as unclear in report, instead the daily dose for adults set to [redacted] mg/day; 4. Post-progression utility independent of treatment ([redacted] for larotrectinib and comparator); 5. Paediatric dose adjustment of larotrectinib (as per ERG base-case); 6. Weibull PFS; 7. Gompertz OS	**£29,077**	**£30,888**
Scenario 2 (without NTRK testing costs)		**£26,466**	**£28,276**
Scenario 3 (with NTRK testing costs) * *ERG response based survival model (as per scenario 2), and further assume that the mean discounted*	1. ERG BHM ERG partitioned response model, ORR=57%; 2. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days (in contrast to no administration costs in the company's submission); 3. Wastage costs assuming patients receive a 28 days' supply of larotrectinib (not implemented as unclear in report, instead the daily dose for adults set to [redacted] mg/day;	**£45,111**	**£48,161**

Scenario	Model settings	ICER Feb 2020 PAS (per QALY)	ICER Feb 2020 PAS ERG** (per QALY)
Company submitted base case	-	**£16,155**	
post-progression survival for larotrectinib is the same as for the comparator	4. Post-progression survival equal for larotrectinib and comparator (response-based survival approach) 5. Paediatric dose adjustment of larotrectinib (as per ERG base-case); 6. Weibull PFS; 7. Gompertz OS		
Scenario 3 (without NTRK testing costs)		**£40,713**	**£43,763**
Scenario 4 (with NTRK testing costs) * *ERG response based survival model (as per scenario 2), and further assume that the mean discounted post-progression survival for larotrectinib is the same as the mean discounted overall survival for the comparator*	1. ERG BHM ERG partitioned response model, ORR=57%; 2. Administration cost of larotrectinib £140.82 (NHS reference costs code SB11Z for oral chemotherapy) every 28 days (in contrast to no administration costs in the company's submission); 3. Wastage costs assuming patients receive a 28 days' supply of larotrectinib (not implemented as unclear in report, instead the daily dose for adults set to [redacted] mg/day; 4. Post-progression survival equal to OS for comparator (response-based survival approach) 5. Paediatric dose adjustment of larotrectinib (as per ERG base-case); 6. Weibull PFS; 7. Gompertz OS	**£37,933**	**£40,342**
Scenario 4 (without NTRK testing costs)		**£34,328**	**£36,827**

Abbreviations: BHM; Bayesian Hierarchal Model, CS; Company submission, ERG; Evidence review Group, GMI; Growth modulation index, NTRK; Neurotrophic Tyrosine Receptor Kinase, NHS; National Health Service, ORR; Overall response rate, OS; Overall survival, PFS; Progression-free survival, QALYs; Quality adjusted life years, ICER; Incremental cost-effectiveness ratio. * Based on ERG's NTRK testing cost estimate by NHS England (average £6,800 per patient treated with larotrectinib). **Setting the prescribing pattern of larotrectinib to once every 4 weeks and the adult daily dosage to [redacted]