NICE National Institute for Health and Care Excellence

NICE guidance

Entrectinib for treating NTRK fusion-positive solid tumours

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Entrectinib is recommended for use within the Cancer Drugs Fund as an option for treating neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumours in adults and children 12 years and older if:

- the disease is locally advanced or metastatic or surgery could cause severe health problems and
- they have not had an NTRK inhibitor before and
- they have no satisfactory treatment options.

It is recommended only if the conditions in the managed access agreement for entrectinib are followed.

1.2 This recommendation is not intended to affect treatment with entrectinib that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children and young people, this decision should be made jointly by the clinician and the child or young person or their parents or carers.

Why the committee made these recommendations

There is no standard treatment for NTRK fusion-positive solid tumours, so current treatment is based on where in the body the cancer starts. Entrectinib is a histology-independent treatment. This means that it targets a genetic alteration, NTRK gene fusion, that is found in many different tumour types irrespective of where the cancer starts.

Evidence from trials suggests that tumours with NTRK gene fusions shrink in response to entrectinib, but longer follow up is needed. It is difficult to know how well entrectinib works because it has not been compared with other treatments in trials. Also, there is evidence that entrectinib works well for some types of NTRK fusion-positive tumour, but little or no evidence for other types.

The cost-effectiveness estimates for entrectinib are uncertain because of limitations in the data. Some of these estimates are higher than what NICE normally considers an acceptable use of NHS resources so entrectinib cannot be recommended for routine use in the NHS.

Collecting more data on entrectinib would help to address some of the uncertainty in the evidence. Entrectinib has the potential to be cost effective given the company's commercial offer as part of a managed access agreement and using the diagnostic testing costs provided by NHS England. Therefore, entrectinib is recommended for use in the Cancer Drugs Fund.

2 Information about entrectinib

Marketing authorisation indication

2.1 Entrectinib (Rozlytrek, Roche) is indicated as monotherapy for the 'treatment of adult and paediatric patients 12 years of age and older, with solid tumours expressing a neurotrophic tyrosine receptor kinase (NTRK) gene fusion:

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity and
- who have not received a prior NTRK inhibitor
- who have no satisfactory treatment options'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price for entrectinib is £5,160.00 per 90-tablet pack of 200 mg tablets (excluding VAT, company submission). The company has a commercial arrangement. This makes entrectinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Roche, a review of this submission by the evidence review group (ERG), NICE's technical report, and responses from stakeholders. See the committee papers for full details of the evidence.

The appraisal committee was aware that several issues were resolved during the technical engagement stage, and agreed that it was appropriate to include people with primary central nervous system (CNS) tumours and children in the population included in the economic modelling (issue 8, see technical report page 35).

It recognised that there were remaining areas of uncertainty associated with the analyses presented (see technical report, table 12, page 61), and took these into account in its decision making. It discussed the following issues (issues 1 to 7 and 9 to 23), which were outstanding after the technical engagement stage.

NTRK gene fusions

Entrectinib targets a genetic mutation rather than a tumour type and there are challenges in appraising it

3.1 Traditional oncology approaches treat tumours based on their type. More recently, targeted therapies based on the tumour's genetic information have been used for some indications. Entrectinib targets solid tumours with a neurotrophic tyrosine receptor kinase (NTRK) gene fusion. Because many tumour types respond to it, the company considers entrectinib to be 'tumour-agnostic' or 'histology-independent'. NTRK gene fusions may be able to drive tumour growth, so targeting treatment to the cause of the disease could mean higher rates of response to therapy and potentially better outcomes. The committee accepted that it was expected to appraise entrectinib within its marketing authorisation using the framework currently set out by NICE. But it recognised the challenges of appraising histology-independent treatments within the NICE single technology appraisal process.

The prevalence of NTRK gene fusions in England is unknown but collecting further data could help address this

3.2 The prevalence of NTRK gene fusions is uncertain. Estimates reported in the literature are between 0.25% and 0.31% in adults and between 0.34% and 0.49% in children and young people. NTRK gene fusions have high prevalence in some rare cancers such as mammary analogue secretory carcinoma, infantile fibrosarcoma and secretory breast cancer. But there is low prevalence in some of the more common cancers such as colorectal cancer and non-small-cell lung cancer. The company submission included a calculated prevalence estimate for each tumour type based on a weighting of prevalence estimates from the literature and data held by the company. The company provided data from the Foundation Medicine Incorporated (FMI) dataset that included data based on next generation sequencing of adult and children's solid tumour samples using the FMI next generation sequencing platform. The ERG estimated the prevalence of NTRK fusions in each tumour type included in the database. There is considerable variation between tumour types, with prevalence estimates ranging from less than 1% to 100% for the tumour types included in the dataset. The committee understood that the ERG's estimates were more likely to be generalisable to clinical practice because they were sourced from a large database and seemed to be the most robust data available currently. The committee concluded that the prevalence estimates from the FMI database were reasonable for decision making but recognised that there was some uncertainty around the true prevalence of NTRK gene fusions in England. Further data collection in clinical practice could mitigate some of this uncertainty.

NTRK fusion-positive solid tumours are not well characterised and the prognostic effect of NTRK gene fusions is unknown

3.3 Everyone included in the entrectinib trials had an NTRK fusion-positive tumour and 20.4% of the entrectinib efficacy population had CNS metastases. Only a small proportion of people in the comparator dataset were likely to have NTRK gene fusions and the prevalence of CNS metastases in the comparator population was unknown. The company included a scenario analysis in its submission. In the analysis the company applied a hazard ratio calculated from published overall survival

data on people with colorectal cancer who had either an NTRK, receptor tyrosine kinase (ROS1) or anaplastic lymphoma kinase (ALK) genetic alteration. It used this to adjust the comparator data to account for people with NTRK fusion-positive solid tumours potentially having a poorer prognosis than people with solid tumours that were not NTRK fusion-positive. At the technical engagement stage the company provided a systematic literature review that did not find any further evidence to support its claim that people with NTRK fusion-positive solid tumours have a worse prognosis than people with tumours without the genetic alteration. The committee agreed that there was not enough evidence available about whether NTRK gene fusions affect prognosis. The company also did a scenario analysis to adjust for the effect of CNS metastases in the comparator arm. The ERG explained that the prevalence of CNS metastases in the comparator data was not widely reported in the clinical trials so any adjustment to the comparator arm was uncertain. It was not possible to report characteristics that are commonly prognostic such as age and Eastern Cooperative Oncology Group performance status, so the committee considered it uncertain whether the 2 arms were comparable. The committee considered that it would be appropriate to adjust the analysis to include factors that are known to affect prognosis but concluded that the evidence was too limited to do so.

Treatment pathway and comparator

There is no defined clinical pathway for people with NTRK fusion-positive solid tumours

3.4 There is no defined clinical pathway for people with NTRK fusion-positive solid tumours. Treatment currently follows care guidelines for specific tumour types. The committee understood that genomic testing to identify NTRK gene fusions was not routinely carried out for all of the different tumour types (see section 3.8). Until routine genomic testing is established in clinical practice, the people most likely to benefit from targeted therapy cannot be offered different treatment options to people with the same type of solid tumour but without the NTRK gene fusion. Some of the tumour types with NTRK gene fusions have an established

treatment pathway with many treatment options available, such as colorectal cancer and non-small-cell lung cancer. However, other tumour types, including mammary analogue secretory carcinoma and cholangiocarcinoma, have few treatment options available for locally advanced and metastatic disease. The patient experts noted that for quadruple negative gastrointestinal stromal tumours there were no standard treatment options. They explained that people who have a solid tumour with a gene alteration would want a targeted treatment. The aim of treatment for some inoperable tumour types would be to shrink the solid tumour so that surgery might be a treatment option. The committee concluded that people with NTRK fusion-positive solid tumours would value new treatment options.

Entrectinib is positioned as last-line therapy in the treatment pathway

3.5 The marketing authorisation specifies that entrectinib should only be used if there are no satisfactory treatment options, that is, for which clinical benefit has not been established, or when such treatment options have been exhausted. The Cancer Drugs Fund clinical lead explained that entrectinib should be used after all NHS commissioned treatments, because these treatments have an established clinical benefit. The company submission was broader than the marketing authorisation because for some tumour types (soft-tissue sarcoma, pancreatic cancer, non-small-cell lung cancer, breast cancer, thyroid cancer, colorectal cancer and neuroendocrine carcinomas) people had treatment before other treatments for locally advanced or metastatic disease. This was because the submission was developed before input from the regulator on the wording of the marketing authorisation. In the entrectinib clinical trials, a large proportion of patients had entrectinib for untreated disease or after 1 previous treatment. The clinical experts explained that if people with NTRK fusion-positive solid tumours had to have treatment with all NHS commissioned therapies before entrectinib then the solid tumours were more likely to be resistant to treatment. Entrectinib would be a treatment option for fewer people if it was used as a last-line therapy because some people would not be well enough to have it after other treatment options. The clinical experts noted that oncologists prefer to use targeted therapies as early as possible in the treatment pathway.

The committee noted that entrectinib's clinical trial evidence may not be generalisable to its use in clinical practice as a last-line treatment option. The Cancer Drugs Fund clinical lead explained that people with rarer cancers that have a high prevalence of NTRK gene fusions may be more likely to have entrectinib as an earlier-line treatment option given that other treatment options are limited (see section 3.4) or may not have an established clinical benefit. This would be different for people with tumour types that have an established treatment pathway and different treatment options. For these tumour types it is likely that, for locally advanced or metastatic solid tumours, entrectinib will be a treatment option only after all NHS commissioned treatments in the treatment pathway.

Best supportive care is the appropriate comparator

3.6 The company's clinical trials were single arm, so did not include a comparator arm (see section 3.11). The ERG explained that because the wording of the marketing authorisation was broader at the time of the company's submission, it was reasonable to include NICE-recommended treatments as comparators for some tumour sites. Entrectinib should be positioned as a treatment option after all NHS commissioned treatments (see section 3.5) so the committee noted that the appropriate comparator should be best supportive care. Best supportive care was included as a treatment option in the company's blended comparator arm for colorectal cancer, thyroid cancer and neuroendocrine tumours only. For some of these tumour sites NICE-recommended treatments were also included as treatment options. The committee concluded that best supportive care was the appropriate comparator for the appraisal given that the marketing authorisation stated that entrectinib should only be used if there are no satisfactory treatment options.

Diagnosis

The diagnostic pathway for NTRK fusions has implications for identifying patients and on diagnosis costs

3.7 All solid tumour types can potentially have an NTRK gene fusion although

they are rare in common tumour types (see section 3.2). Therefore, many people would need screening to identify who would benefit from entrectinib. Currently, NTRK testing is not routinely done in the NHS for all solid tumours. However, it is available for mammary analogue secretory carcinoma and secretory breast carcinoma with immunohistochemistry techniques (a method using antibodies to detect the gene fusion protein). Whole genome sequencing (a method of determining the whole DNA sequence of a cancer, used for discovering mutations) can also identify NTRK gene fusions and it is available for children's cancers and sarcomas. However, confirmation of the results with another DNA or RNA test is needed (for example next generation sequencing, which is a faster method of sequencing targeted regions of the cancer's DNA). The committee concluded that the diagnostic pathway for NTRK gene fusions was important, with implications for identifying patients and on costs of diagnosis.

The diagnostic pathway is uncertain until NHS England establishes a national service for genomic testing of all advanced solid tumours

3.8 The Cancer Drugs Fund clinical lead explained that NHS England is currently establishing a national service for cancer genomic testing to replace all local testing. It involves setting up 7 laboratory hubs across England to do genomic testing by next generation sequencing and interpret all results. Until the laboratory hubs are fully established, next generation sequencing will be done after all NHS commissioned treatment options have been tried. When the hubs are fully established, next generation sequencing to identify gene alterations, including NTRK gene fusions, will be done when locally advanced or metastatic solid tumours are first diagnosed. The Cancer Drugs Fund clinical lead estimated that 100,000 solid tumours would be tested per year once the service is fully established. He noted that other targeted therapies would likely become available soon for different diseases and genomic testing would also be needed before these treatments are used. The committee acknowledged the ongoing developments in genomic testing practice to identify NTRK fusion-positive solid tumours. It considered that the rapid change to the diagnostic testing pathway being led by NHS England was a unique situation. The committee concluded that the diagnostic testing

pathway was uncertain until NHS England establishes a national service for cancer genomic testing.

Diagnostic techniques will improve as the genomic laboratory hubs validate their techniques and NTRK gene fusions are better characterised

3.9 Because the genomic laboratory hubs were not yet operational, there was no single representative NHS-based test that would allow measurement of diagnostic accuracy. The Cancer Drugs Fund clinical lead explained that the genomic laboratory hubs were putting a lot of resources into ensuring high diagnostic accuracy in their testing procedures. The committee noted that high sensitivity and specificity of a diagnostic test minimises the risk of false results. If specificity was not high then there was a greater chance of a solid tumour testing positive for an NTRK gene fusion when an NTRK gene fusion was not present. Solid tumours that do not have an NTRK gene fusion are not expected to respond to entrectinib and this could result in poorer clinical outcomes than with a different treatment option. High diagnostic accuracy is particularly important when screening tumour types that have a known low prevalence of NTRK gene fusions such as lung and colorectal cancer. The clinical experts explained that it was essential that a combined DNA and RNA-based next generation sequencing panel is used in clinical practice to identify people with NTRK fusion-positive solid tumours. This was because a DNA-based panel may identify NTRK gene fusions that, when treated with entrectinib, would not lead to the expected clinical outcomes. They explained the importance of correctly interpreting the results of the genomic test to identify the significant NTRK gene fusions. The committee noted that the genomic laboratory hubs were very aware of the importance of high diagnostic accuracy, especially given that some tumour types have very low prevalence of NTRK gene fusions. The committee considered that this is an evolving field and that diagnostic techniques would improve as the genomic laboratory hubs validate their techniques and NTRK gene fusions are better characterised (see section 3.3). The committee concluded that diagnostic accuracy was very important and that a period of access in the Cancer Drugs Fund could allow the genomic laboratory hubs to implement testing more quickly.

Clinical evidence

NTRK gene fusions have been identified in primary CNS and children's tumours so including them in the population is appropriate

3.10 The marketing authorisation includes people with primary CNS tumours and children (on 28 May 2020, the Committee for Medicinal Products for Human Use announced that this would be children over 12 years). The company updated its submission at the technical engagement stage. It used data from 5 adults with primary CNS tumours and 7 children with NTRK gene fusions in the efficacy population that were included in the company's clinical trials. The committee considered it appropriate to include these data in the analysis because it increased the generalisability of the evidence base to the population likely to be seen in clinical practice. The population of children included in the clinical trial was small and it did not represent all children's tumours that were known to have NTRK gene fusions. Some patients in the trials were under 12 years and it is likely that many children in clinical practice will be under 12 years, so would not be eligible for entrectinib because of the marketing authorisation's age restriction. However, the committee considered these results would likely be comparable with results from older children. It noted also that there was considerable uncertainty because of the very low number of children in the trials and distribution of tumour types. The committee concluded that it was appropriate to include people with primary CNS tumours and children in the analyses because they are part of the population covered by entrectinib's marketing authorisation.

The key clinical evidence comes from a pooled analysis of 4 single-arm clinical trials and is appropriate for decision making

3.11 The company did a pooled analysis of results for 54 adults from 3 clinical trials (ALKA, STARTRK-1 and STARTRK-2) in its original submission. STARTRK-2 is an ongoing phase 2 basket trial for people aged 18 years and over with advanced or metastatic solid tumours that have an NTRK, ROS1 or ALK gene fusion. Basket trials are trials that include patients who

have different types of cancer but the same gene mutation. The baskets in the STARTRK-2 study were based on molecular targets (ALK, ROS1 and NTRK) rather than on tumour type for each molecular target. The ERG noted that this was different to a typical basket trial design. STARTRK-2 contributed 51 patients to the pooled analysis. ALKA contributed 1 patient to the pooled analysis and STARTRK-1 contributed 2 patients. Both ALKA and STARTRK-1 are ongoing phase 1 ascending dose and dose escalation studies. At the technical engagement stage the company updated its entrectinib dataset to include 66 people (see section 3.10). The children's data were collected in the STARTRK-NG trial, a dose escalation and expansion study evaluating the effect of entrectinib in children, adolescent and young adults aged 2 to 22 years. The committee noted the small patient numbers from each of the trials making up the pooled analysis, and that the trials were single arm and did not include a control group. The Cancer Drugs Fund clinical lead considered it reasonable to pool the 4 entrectinib studies to maximise the patient numbers included in the analyses. The clinical trial evidence included only 13 tumour types: sarcoma, non-small-cell lung cancer, mammary analogue secretory carcinoma, breast, thyroid, colorectal cancer, neuroendocrine tumours, pancreatic cancer, gynaecological cancers, cholangiocarcinoma, CNS primary, infantile fibrosarcoma and paediatric melanoma. Also, each tumour type was represented by between 1 and 13 patients. Given the rarity of the gene fusion, the committee considered that the evidence base was appropriate for decision making. But it acknowledged that further data collection was possible because the company's trials were ongoing.

Entrectinib could be clinically effective, but its survival benefit is difficult to measure because of limitations in the trial data

3.12 The pooled analysis of 66 people across 13 tumour types (see section 3.11) showed a clinically relevant overall response rate across tumour types (exact results are confidential and cannot be reported here). However, there was considerable uncertainty about the extent to which the response translated into clinically meaningful survival benefits. At the most recent data-cut, median follow up was short and the survival data were immature. Also, the number of patients with specific cancers was very small so there was uncertainty in the robustness of all survival

data. The Cancer Drugs Fund clinical lead noted that entrectinib was active in patients with CNS metastases with a similar response rate in the brain to that seen systemically in all patients in the pooled analysis. However, the small patient numbers and short follow up were noted. The committee saw that there was no direct evidence of entrectinib's effectiveness compared with established management. It concluded that entrectinib could be clinically effective, but the limited data for each of the tumour types, the immature survival data and the lack of trial data directly comparing entrectinib with established management meant the size of this benefit was difficult to measure.

The population eligible for entrectinib is broader than the trial population so entrectinib's clinical effectiveness in some groups is unknown

3.13 There was limited evidence available on tumour types that have NTRK fusions. The clinical evidence for entrectinib was limited to the 13 tumour types included in the company's clinical trials. The ERG's clinical advisers suggested that it was plausible that NTRK gene fusions could be present in over 400 tumour types. The ERG used a Bayesian hierarchical modelling framework (see section 3.15) to explore the expected probability of response to entrectinib in tumour types not represented in the trial data. The results showed a very wide confidence interval around the probability of response for tumour types not included in the trial. This showed the high uncertainty around the response (exact results are confidential and cannot be reported here). The committee considered that the lack of any data for many other tumour sites meant there was substantial uncertainty about entrectinib's clinical and cost effectiveness for all those potentially eligible for treatment as defined by the marketing authorisation. The committee acknowledged that the ERG's analysis gave a reasonable estimate of the response rates for tumour types for which there were no data. It understood that the uncertainty would only be resolved through further data collection, including for other tumour types not already included in the clinical trials. But it noted that patient numbers could still be a limitation. The committee understood the challenges of appraising a histology-independent treatment when the population covered by the marketing authorisation was broader than the evidence base. It concluded that there was uncertainty about

entrectinib's clinical effectiveness for tumour types that were not included in the clinical trials. Until further data are reported, the clinical benefit of using entrectinib in the NHS cannot be confirmed.

The company assumes the same response to entrectinib for all tumour types but this is inappropriate

3.14 There are several biological reasons why heterogeneity, or a difference, in tumour response to entrectinib might be seen. For example, tumour response might be different by histology, by NTRK gene fusion or fusion partner, by the presence of codrivers of the disease and by age (for example, for children's indications). The company assumed that each of the solid tumour types would have the same response rate when treated with entrectinib and generated a pooled response estimate across each of the tumour types included in the efficacy dataset. This approach did not take into account the potential for heterogeneity in response across different tumour types and fusion partner. There was considerable uncertainty in the level of heterogeneity in response rates across tumour types (exact results are confidential and cannot be reported here). The company did not explore any alternatives to this assumption. The committee concluded that it was not appropriate to assume that the same level of response would be seen across all tumour types eligible for treatment with entrectinib.

The ERG's approach explores heterogeneity in tumour response, but more data would help investigate this further

3.15 The ERG used a statistical modelling framework, Bayesian hierarchical modelling, to explore the potential heterogeneity in response across the 13 tumour types included in the company's dataset. This used the tumour type to define each basket and allowed borrowing of information across baskets by assuming that response rates were exchangeable, rather than the same across baskets. Tumour types with few patients borrowed more information than tumour types with more patients. Using this method, the ERG found that the estimated mean response rate across all tumour types was similar to the response rate seen when the company assumed an equal response. The company made the data available for survival outcomes by tumour type for the ERG to do this

analysis on the progression-free and overall survival data. The ERG considered the survival data not to be robust enough to explore variability in overall and progression-free survival so these data could not be included in the company's partitioned survival model. The ERG noted that it was unclear whether the Bayesian hierarchical modelling would give useful survival estimates given the small number of patients with each of the tumour types and that the data were immature. The ERG's analyses showed the potential for heterogeneity between tumour types but had small patient numbers in each of the tumour types included in the analysis. The committee acknowledged that the results of the ERG's Bayesian hierarchical modelling approach were similar to the company's approach (see section 3.14). The committee considered the wide confidence intervals around the response estimate and the possibility that some tumour types could have response rates that differed significantly from the pooled estimate. It understood that further data collection would increase the patient numbers for each of the tumour types and this would help improve the robustness of the analysis. More mature survival data would allow heterogeneity in the survival outcomes to be explored. The response estimates were similar when some adjustment for heterogeneity was included (the ERG's Bayesian hierarchical modelling approach) and when it was not (the company's approach). The committee concluded that this is an outstanding uncertainty that needs to be explored further when more data are available.

The trial population is not generalisable to the population in clinical practice in England

3.16 The company assumed that the distribution of the 13 tumour sites in its dataset reflected the distributions seen in clinical practice in England. The most frequently represented solid tumour types in the trial evidence were sarcomas, non-small-cell lung cancer, salivary gland tumours (mammary analogue secretory carcinoma) and breast cancer. The company used this distribution to estimate a weighted set of outcomes for the comparator arm in its base-case analysis. The ERG was concerned that the estimate of cost effectiveness was being driven by the proportion of tumour types included in the company's dataset. The Cancer Drugs Fund clinical lead highlighted that the distribution of

tumour types in the population in England who would have treatment would differ significantly from that in the entrectinib clinical trial population. In particular, he noted the high proportion of people included in the entrectinib clinical trials who had mammary analogue secretory carcinoma. The ERG estimated the yearly prevalence of NTRK fusion-positive solid tumours in England. It noted that secretory breast carcinoma, sarcoma and mammary analogue secretory carcinoma were over-represented in the company's dataset. The ERG determined an alternative distribution of tumour types using the FMI database, which the committee considered the most appropriate source of data (see section 3.2). The ERG considered this dataset to be more representative of clinical practice because it was based on a larger sample than the company's original estimate. The company did not provide the data needed for the ERG to adjust the distribution of tumour types in the entrectinib arm as well as the comparator arm. At the technical engagement stage the company noted that the likely distribution of NTRK gene fusion-positive tumour types in England may only be definitively known once comprehensive next generation sequencing-based testing was implemented in an unbiased way for all advanced and metastatic cancer diagnoses. The committee recalled that there was uncertainty in the analysis about the distribution of tumour types in the company's and ERG's analyses (see section 3.14 and section 3.15). The committee concluded that the trial population was not generalisable to the population who would have entrectinib in clinical practice in England.

Indirect treatment comparison

The company's approach to the comparator arm is pragmatic, but other methods should be considered

3.17 The company constructed a comparator arm to compare clinical effectiveness between entrectinib and established management. It generated a comparator arm by identifying overall and progression-free survival data for established management. It did this by searching NICE Pathways for NICE-recommended comparators for each of the tumour types included in the entrectinib clinical trials. Median progression-free and overall survival for each tumour type were averaged and then pooled

to calculate mean overall progression-free and overall survival across all tumour types, weighted by the distribution of each tumour type in the trial population. For some tumour types tumour-site specific data were not available, so an average from the other tumour types was used. The ERG considered the company's methods to identify, select and combine the comparator data to be inappropriate. It considered the comparator data in the company model to be highly unreliable. The ERG considered the company's approach to be intuitive, but the comparator population:

- was not consistent with the entrectinib population for CNS metastases and other potential prognostic factors (see section 3.3)
- did not reflect the population seen in clinical practice if the comparators had not been selected at the appropriate line of treatment (see section 3.6).

The ERG suggested 2 further approaches, a previous line of treatment approach (see section 3.18) and a response-based approach (see section 3.19). The committee recognised the difficulty in constructing a comparator arm for this appraisal. It concluded that the company's original approach was pragmatic but other methods should also be considered in the committee's decision making.

The company's previous line of treatment approach is a reasonable alternative to generating comparator data

3.18 The company did a previous line of treatment analysis (referred to by the company as an intra-patient analysis) at the technical engagement stage. This was as a confirmatory analysis to their original pooled comparator approach. The company assessed the time to next treatment for 31 patients included in the STARTRK-2 study who had a treatment before entrectinib. The time to next treatment for the treatment administered directly before entrectinib was considered to be a proxy for progression-free survival. The company acknowledged that this may have overestimated progression-free survival because treatment was unlikely to start exactly at the point of progression with the previous treatment. The company overcame the limitation that 10 patients included in this analysis did not have a documented reason for stopping treatment by doing the same analysis for those who did have a

documented reason. The results showed that the median time to next treatment was broadly similar to the median progression-free survival estimate derived for the company's blended comparator using its pooled approach. The ERG acknowledged that the company's previous line of treatment analysis may have produced a more reliable progression-free survival estimate in the comparator arm than the original modelled comparator or the ERG's response-based analysis (see section 3.19). But the ERG highlighted that there were 2 assumptions that must hold for this analysis to be valid, which it considered to be strong and hard to verify. The ERG also highlighted that to understand the effect of this modelling approach on the incremental cost-effectiveness ratio (ICER), the data would need to be included in the economic model and an extrapolation function applied. The committee was aware of the limitations of this approach. But, it concluded that it was a reasonable alternative to generating the comparator data and should also be considered in the committee's decision making.

The ERG's exploratory response-based approach is limited by the generalisability of the trial data to clinical practice

3.19 The results of the ERG's response-based approach were presented as an exploratory analysis. This approach involved taking the survival data for the people whose tumours did not respond from the entrectinib dataset and using these data for the comparator arm. The company considered the number of people whose tumours did not respond to be too small to provide a meaningful comparator sample. So, the ERG's method had some issues, including:

- the people whose tumours did not respond potentially having a different prognosis to those whose tumours did respond
- whether the effect of different subsequent therapies could be included in the clinical data
- the generalisability of the population to the population likely seen in clinical practice, particularly given that the clinical trial population was not generalisable (see section 3.16)
- entrectinib being given at earlier points in the treatment pathway in the clinical

trials than it would be in clinical practice (see section 3.5).

The committee understood that, as with the other approaches, data availability was an issue given the small patient numbers in the entrectinib clinical trials and the immaturity of the data. It concluded that the ERG's exploratory response-based approach was a reasonable alternative to generate comparator data. Additional data would help improve its robustness, but issues around generalisability could not be resolved, which was a major limitation of this analysis. The committee concluded that this approach was a reasonable alternative to generating comparator data. But, because of the limitations in generalisability, it was suitable only for exploratory analysis with current data.

Economic model

All modelling approaches for decision making are uncertain

3.20 The company presented a 3-state partitioned survival model (progression-free, progressed disease and death) to estimate the cost effectiveness of entrectinib compared with established management. The model used data on overall and progression-free survival from the entrectinib clinical trials for the entrectinib arm. The established management arm was modelled using the data from the company's approach to modelling the comparator arm (see section 3.17). The company's model did not account for tumour types not represented in the entrectinib clinical trials (see section 3.15). The committee noted that the different approaches and methods used to construct the comparator arm for this appraisal (see section 3.17, section 3.18 and section 3.19) would affect the choice of model structure. The ERG explained that a major limitation of the company's model structure was that it could not account for tumour types not included in the entrectinib clinical trials (see section 3.15). Also, it did not have the functionality to produce an ICER for each tumour type individually, so produced only a single ICER. The ERG did some exploratory analysis using a response-based model. This approach distinguished between people whose tumours responded to treatment and people whose tumours did not respond for clinical effectiveness inputs as well as for health-related quality of life and the costs of care. The ERG's response-based approach used data from

people whose tumours did not respond as a proxy for people not having an active treatment. Survival in the entrectinib arm was estimated as a weighted average of survival for the people whose tumours responded and those whose tumours did not, weighted by the estimated response rate derived from the ERG's Bayesian hierarchical model (see section 3.15). The ERG's response-based model allowed for results to be generated for each tumour type individually and could also account for tumour types that were not included in the entrectinib clinical trials. The committee considered that when more data were available the different model structures could be explored more fully. It concluded that each of the modelling approaches had limitations and uncertainties.

Survival extrapolations

The company's exponential extrapolation is appropriate to model overall and progression-free survival, but other extrapolations are also plausible

3.21 The entrectinib clinical trials are ongoing so data on overall survival were incomplete. To extrapolate overall survival for entrectinib and the established management comparator arm, the company fitted an exponential curve to the data. The ERG preferred the Weibull distribution to extrapolate overall and progression-free survival data because it gave a more clinically plausible balance between pre- and post-progression survival. The ERG explained that there was no difference in statistical fit between this distribution and the exponential distribution to extrapolate overall and progression-free survival. The exponential distribution gave a longer duration of survival in the post-progressed health state than in the pre-progressed health state. At the technical engagement stage the company did a scenario analysis using the proxy Weibull distribution in the comparator arm and the Weibull distribution in the entrectinib arm. The ERG explained that the most appropriate method to generate the extrapolated survival curves for the comparator arm would have been to extract the Kaplan–Meier curves from each of the source NICE technology appraisals included in the company's pooled comparator arm and to use the committee's most appropriate distribution for each of the appraisals. The committee noted that the survival data from the clinical

trials were very immature and this made it challenging to select the most appropriate extrapolation function. The committee concluded that the exponential extrapolation was appropriate but other extrapolation functions were also plausible. It also noted that the trials were ongoing and follow-up survival data could reduce this uncertainty if all plausible extrapolations are considered after a period of further data collection.

Utility values in the economic models

The company's utility estimates are unlikely to be generalisable to clinical practice given entrectinib's position in the treatment pathway

3.22 The company's utility value in the pre-progressed health state in the entrectinib arm was taken from the EQ-5D-3L data from the STARTRK-2 study. The utility values for the comparator arm were derived from a single NICE technology appraisal for each tumour type included in the entrectinib clinical trials. A single utility value was calculated for each health state by calculating the average utility value, weighted by the distribution of tumour types included in the clinical trial; 0.73 for progression-free and 0.59 for progressed disease. The company considered its utility value for the progressed disease health state derived from the STARTRK-2 EQ-5D-3L data to be implausible because it was higher than the pre-progressed value. The same utility value was used in both arms for the progressed disease health state. In the STARTRK-2 study a reasonable proportion of people had entrectinib as first-line treatment. The committee agreed that entrectinib's position was now as a last-line treatment option (see section 3.5). It recognised that the utility value in the pre-progressed health state may no longer be generalisable to clinical practice because it was likely to be an overestimate. The ERG also highlighted that the company's choice of NICE technology appraisal for the comparator arm utility value may have biased the cost-effectiveness analysis. This was because the selected utilities reflected a specific line of therapy and entrectinib's position was last line. The committee concluded that the utility estimates were unlikely to be generalisable to clinical practice because entrectinib's position in the treatment pathway was likely to be as a last-line treatment option.

The size of difference in the pre-progressed utility values between arms is uncertain

3.23 The company used a higher utility value in the pre-progressed health state in the entrectinib arm (exact value is confidential and cannot be reported here) than in the comparator arm (0.73). The company justified this because entrectinib is an oral treatment with a more convenient administration and better safety profile than the comparators, which are mostly cytotoxic chemotherapies. Best supportive care was the appropriate comparator (see section 3.6) so entrectinib's safety profile compared with best supportive care was unlikely to give a higher utility score. The ERG highlighted the lack of evidence to justify the assumption to use different values in each arm for the pre-progressed health state. It considered there was considerable uncertainty about the size of any difference. The Cancer Drugs Fund clinical lead noted that equal utility values should be used in the progression-free health state. The committee recognised the uncertainty in the utility values given entrectinib's position in the treatment pathway as a last-line treatment option. It concluded that there was some uncertainty about the size of difference in the pre-progressed utility values between arms.

Subsequent therapies

It is not appropriate to include subsequent therapies in the analysis if entrectinib is a last-line treatment option

3.24 In the entrectinib clinical trial a reasonable number of people had subsequent therapy after entrectinib and this was included in the company's analysis. The subsequent therapies included targeted therapies. No subsequent therapies were included after established management in the comparator arm. The company modelled the duration of treatment with subsequent therapies from progression until death. The ERG considered it overly pessimistic to assume that people would have subsequent therapies from progression until death and instead assumed a treatment duration of 6 months, about half of the post-progression duration. The committee considered entrectinib's position in the treatment pathway as a last-line treatment option (see section 3.5). It

agreed that if subsequent therapies were to be given after entrectinib, these would not be active treatments in which clinical benefit had been established. This was because these treatments would likely have been tried before entrectinib. The committee concluded that it was not appropriate to include subsequent therapies in the analysis if entrectinib was a last-line option in the treatment pathway.

Resource use and costs

It is appropriate to include diagnostic testing costs in the economic model

3.25 The company attempted to capture the diagnostic testing pathway and associated costs in its analysis. It included a 2-stage approach to testing for cancers when biomarker screening is already done in clinical practice (for colorectal, non-small-cell lung, breast and thyroid cancers) or when no molecular testing is done (for neuroendocrine, pancreatic and gynaecological tumours and cholangiocarcinoma). This included an immunohistochemistry test, which if positive was followed by a next generation sequencing test. The ERG considered the company's approach to testing to be broadly plausible. For cancers that have whole genome sequencing (see section 3.7), the ERG's clinical advisers noted that an RNA-based next generation sequencing test would be needed after whole genome sequencing to confirm an NTRK fusion-positive tumour. The ERG did not consider it appropriate to include the costs of testing in the comparator arm for tests that did not identify NTRK gene fusions. It also noted that the costs of testing for NTRK gene fusions in lung cancer samples would be negligible beyond the cost of genomic testing already done in clinical practice. The committee acknowledged the difficulty in determining the potential diagnostic screening pathway and associated costs at a time when there are rapid developments in the NHS. The clinical experts explained that immunohistochemistry testing was considered to be the optimal screening method to identify NTRK fusion-positive tumours in European and US guidelines. The Cancer Drugs Fund clinical lead explained that NHS England does not intend to invest further in immunohistochemistry testing given the current service redesign towards a national service for genomic testing (see section 3.8).

The committee concluded that the company's diagnostic testing approach was reasonable because it reflected current clinical practice but recognised that NHS England was rapidly moving towards a national service for cancer genomic testing. The committee understood that the NICE methods guide was not designed to address a system-wide change in diagnostic techniques and the cost of testing would depend on NHS England's testing strategy. The company included testing costs in its economic model for its 2-step approach and the ERG explored the effect of including different testing strategies on entrectinib's cost effectiveness. The committee recognised that NHS England is rapidly moving towards a national service for cancer genomic testing and noted NHS England's proposal to implement next generation sequencing-based testing at diagnosis for all locally advanced or metastatic solid tumours. It agreed NHS England's cost per patient with an NTRK fusion-positive tumour should be included in the economic model. The committee understood that this proposal reflected the likely situation in the near future, once the changes to the diagnostic pathway had been established, but considered this approach to be appropriate for decision making. The committee concluded that it was appropriate to include diagnostic testing costs in the economic model.

The economic model should include the costs of oral chemotherapy administration and drug wastage

3.26 The company did not include the costs of oral chemotherapy administration or drug wastage in its economic model. The Cancer Drugs Fund clinical lead noted that the oral chemotherapy administration costs should be included and the ERG incorporated them in its analyses after the technical engagement stage. The ERG added drug wastage to its analysis because a pack with a month's supply would be given to the person taking entrectinib and this would not be reused if treatment stopped before the pack was finished. The company acknowledged in its response to the technical engagement stage that there may be a small amount of drug wastage in clinical practice. However, the company highlighted that in its original submission a dose intensity of 100% was used. This was a conservative assumption because the mean observed dose in the clinical trials was lower. The committee concluded that drug wastage and the costs of oral chemotherapy administration should be

included in the economic model, but it noted these did not have a significant effect on the cost-effectiveness estimates.

The ERG's changes to costs are appropriate but there are some uncertainties

3.27 The company submission included a simplifying assumption for treatment administration costs and healthcare resource use that categorised the different types of treatment into 3 classes: oral, simple intravenous and complex intravenous interventions. The ERG noted that the infusion time varied significantly within the company's categories in its simplifying assumption and that the true effect of the administration costs was an uncertainty in the analysis. The ERG also identified some costs that had not been included in the company's progressed disease health state cost and noted that the company had used the BNF for the costs of the comparator treatments rather than the electronic market information tool (eMIT). The ERG considered the eMIT to be a more accurate and up-to-date indicator of treatment costs and the Cancer Drugs Fund clinical lead noted that this was the appropriate source of treatment costs. At the technical engagement stage the company did scenario analyses, including an updated progressed disease health state cost and comparator treatment costs sourced from the eMIT. The committee considered these scenario analyses to be appropriate for decision making but noted that there were some uncertainties around the administration costs included in the analyses.

End of life

Entrectinib has plausible potential to meet the end-of-life criteria

3.28 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. The company proposed that entrectinib met these criteria for people with a short life expectancy (normally less than 24 months). The end-of-life criteria were not designed for histology-independent treatments and the committee was not shown the data needed to assess if entrectinib met the criteria for people with NTRK

gene fusions specifically. Instead, the committee was shown life expectancy data for people with the relevant tumour type irrespective of NTRK gene fusion status and life extension data estimated from the model. It acknowledged the challenges with the data available, for example:

- the distribution of tumour types in the trials (see section 3.16) and unrepresented tumour types not being included in the clinical evidence (see section 3.11)
- the uncertainty around entrectinib's position in the treatment pathway (see section 3.5)
- the limited survival data available (see section 3.12)
- the prognostic importance of NTRK gene fusions (see section 3.3) and
- the uncertainty about how the survival data was extrapolated (see section 3.21).

The committee considered that most tumour types represented in the trials had overall survival estimates that would meet the short life expectancy criterion. It acknowledged that the overall survival estimates for people with thyroid and neuroendocrine tumours exceeded 24 months. But it considered the positioning of entrectinib as last-line therapy after all NHS commissioned treatments. The committee concluded that entrectinib has plausible potential to meet the end-of-life criterion for short life expectancy for most tumour types included in the entrectinib dataset, as most people with these tumour types have a life expectancy of less than 24 months. The committee noted the uncertainty associated with the short overall survival follow up in the entrectinib clinical trials and the small patient numbers for each tumour type. But it understood that both the company's and the ERG's modelling suggested that entrectinib was associated with an overall survival gain of over 3 months, irrespective of the choice of survival modelling. The committee concluded that entrectinib has plausible potential to meet the end-of-life criteria. But it acknowledged that there was uncertainty in determining both the life expectancy and the exact extension to life given the immaturity of the data and potential for heterogeneity across all of the different tumour types. Further data collection could resolve this uncertainty and the distribution of tumour sites likely to meet the life expectancy criterion.

Cost-effectiveness results

Entrectinib is not recommended for routine use in the NHS

3.29 The company's revised base case after the technical engagement stage gave a deterministic ICER of £49,358 per quality-adjusted life year (QALY) gained for entrectinib compared with established management. This included entrectinib's confidential simple discount but list prices for all other treatments. The company's revised base case included the NICE technical team's preference to include people with primary CNS tumours and children in the base-case population and included the costs of diagnostic testing. The revised base case did not include the committee's preferred assumptions to:

- remove comparator arm testing costs that did not identify NTRK gene fusions and remove testing costs for lung cancer
- use the prevalence estimates for the whole population rather than the population included in the entrectinib trials
- include a confirmatory next generation sequencing test after whole genome sequencing
- explore other plausible survival extrapolation distributions (for example the Weibull distribution for overall and progression-free survival)
- remove second-line therapies in the comparator arm for breast and colorectal cancer and neuroendocrine tumours
- include drug wastage or the costs of oral chemotherapy administration
- use eMIT costs instead of BNF costs for the comparator treatment costs
- use 6 months' duration of subsequent therapy after progression
- include the revised cost of the progressed disease health state.

The committee therefore agreed to use the analyses that included its preferred assumptions. These analyses also included:

- a new commercial arrangement from the company (confidential so cannot be

reported here)

- diagnostic testing at the point of diagnosis of locally advanced or metastatic cancer costed per patient with an NTRK fusion-positive tumour, as provided by NHS England before the committee meeting.

Based on the available evidence, the committee concluded that entrectinib (with the discount agreed in the commercial arrangement) had plausible potential for cost effectiveness if it met the end-of-life criteria. However, it also concluded that the ICER range on which it was basing its decision was associated with substantial uncertainty, particularly in the survival estimates and in modelling a population that was not generalisable to NHS clinical practice. The committee agreed this uncertainty needed to be accounted for in making its judgement about entrectinib's acceptability as an effective use of NHS resources. It acknowledged the ongoing NHS developments and that the company had asked that entrectinib was considered only for use within the Cancer Drugs Fund. The committee concluded that entrectinib could not be recommended for routine use in the NHS.

Cancer Drugs Fund

Further data collection could address uncertainties in the clinical and cost-effectiveness evidence

3.30 Having concluded that entrectinib could not be recommended for routine use, the committee then considered if it could be recommended for treating NTRK fusion-positive solid tumours within the Cancer Drugs Fund. The committee discussed the arrangements for the Cancer Drugs Fund agreed by NICE and NHS England in 2016, noting NICE's Cancer Drugs Fund methods guide (addendum). The company expressed an interest in entrectinib being considered for funding through the Cancer Drugs Fund in its submission. The committee recognised that entrectinib is innovative (see section 3.32) and its use in clinical practice would help accelerate NHS England's developments in genomic testing (see section 3.9). The committee considered whether the clinical uncertainty associated with entrectinib's use could be addressed through collecting more data. More data from the entrectinib clinical trials are expected and

the company also have other data collection activities ongoing. The committee agreed that:

- The ongoing entrectinib clinical trials will provide more mature survival data for people already enrolled in the trials. They may recruit additional patients with solid tumours at sites not already included in the clinical trials, which will provide further data to explore the heterogeneity in response to treatment.
- Real-world evidence collected within the Cancer Drugs Fund through Blueteq, SACT and the molecular dataset may provide further information on the prevalence of NTRK gene fusions, the distribution of tumour types in England, the screening pathway and testing costs and use of subsequent therapies.
- Flatiron data (a US database of real-world clinical outcomes from cancer patients) and the Foundation Medicine genomic database (a US database of genetic data from samples of cancer tissue and blood) may provide data to further explore the heterogeneity in response to treatment and data to explore a matched cohort analysis to construct a comparator arm. It may also provide data to inform the decision about the end-of-life criteria.
- A non-interventional study led by the European Thoracic Oncology Platform will collect utility data for prospective entrectinib patients and may provide data to help inform the decision about the end-of-life criteria.

  When entrectinib's European public assessment report is available, the managed access agreement may be updated to reflect any specific obligations that could inform the guidance review.

Entrectinib meets the criteria to be included in the Cancer Drugs Fund

3.31 Data from the entrectinib trials showed that tumours in people having entrectinib may have good response rates, and there may be an improvement in overall and progression-free survival. The committee acknowledged that it had not seen evidence that fully reflected entrectinib's likely position in the treatment pathway, that is, as a last-line therapy, and that the evidence base was very uncertain. It noted that the company's revised base-case ICER including testing costs for entrectinib compared with established management was within what NICE considers

a cost-effective use of NHS resources if end-of-life criteria are applied. The committee acknowledged that all the ICERs for entrectinib compared with established management were uncertain. But, taking the NHS developments around genetic testing and the company's commercial arrangement into account, it concluded that entrectinib had plausible potential to satisfy the criteria for routine use if this uncertainty could be reduced and genetic testing was fully established in clinical practice. The committee concluded that entrectinib met the criteria to be considered for inclusion in the Cancer Drugs Fund because it showed plausible potential for cost effectiveness at the end of the managed access agreement, when the diagnostic pathway would be fully operational in NHS England. It recommended entrectinib for use through the Cancer Drugs Fund as an option for people with NTRK fusion-positive solid tumours if the conditions in the managed access agreement were followed.

Innovation

Entrectinib is innovative and there are wider benefits to the NHS not captured in the analysis

3.32 The company considered entrectinib to be innovative. The patient and clinical experts agreed because it targets NTRK gene fusion, a new genomic target. The committee considered entrectinib to be innovative because it represents a major change in treating NTRK fusion-positive solid tumours. The committee understood that an important innovation is already underway in the NHS in developing more sophisticated strategies to improve genomic testing in clinical practice. These advances will likely help the uptake of treatments targeted to a gene alteration. The Cancer Drugs Fund clinical lead explained that histology-independent treatments entering the market are accelerating the advances in genomic testing in the NHS. It is estimated that 100,000 solid tumours will be tested per year once the genomic medicine service is fully established, thought to be within the next 2 years. The committee acknowledged that the improvements in genomic testing would bring wider benefits to the NHS and that these benefits have not been captured in the QALY calculation. The committee concluded that entrectinib would be beneficial for

patients, but it had not been presented with any additional benefits that could be specifically attributed to entrectinib that were not captured in the measurement of the QALY.

Equality considerations

There are no equality issues relevant to the recommendations

3.33 The company did not highlight any equality issues. The Cancer Drugs Fund clinical lead noted that there may be issues about access to entrectinib. This is because the genomic testing needed to identify NTRK fusion-positive solid tumours is still being established as a national service (see section 3.8). The committee understood that any variation in access to genomic testing will be resolved in the next 1 to 2 years. The marketing authorisation specifies that entrectinib is a treatment for people of 12 years and over. The company explained that further data for children has been requested by the regulators. However, because the recommendations for entrectinib apply to the whole population in the marketing authorisation, the committee agreed that its recommendations do not have a different effect on people protected by the equality legislation than on the wider population. The committee concluded that there were no relevant equality issues.

4 Implementation

4.1 When NICE recommends a treatment as an option for use within the Cancer Drugs Fund, NHS England will make it available according to the conditions in the managed access agreement. For entrectinib, this will require the necessary diagnostic testing infrastructure to be in place for the testing to be available and any training requirements addressed. This means that, if a patient has an neurotrophic tyrosine receptor kinase (NTRK) fusion-positive solid tumour and the doctor responsible for their care thinks that entrectinib is the right treatment, it should be available for use, in line with NICE's recommendations and the Cancer Drugs Fund criteria in the managed access agreement. Further information can be found in NHS England's Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry. NHS England is setting up 7 genomic laboratory hubs to do the next generation sequencing tests needed to establish if someone is eligible for entrectinib treatment. Until the hubs are fully established, there needs to be a phased introduction of next generation sequencing for people with advanced solid tumours. Over the next 1 to 2 years, next generation sequencing will be done when standard care systemic therapies commissioned by NHS England have failed. Once testing capacity at the hubs is fully established, people will have next generation sequencing when a locally advanced or metastatic solid tumour is first diagnosed.

4.2 Chapter 2 of Appraisal and funding of cancer drugs from July 2016 (including the new Cancer Drugs Fund) – A new deal for patients, taxpayers and industry states that for those drugs with a draft recommendation for use in the Cancer Drugs Fund, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Drugs that are recommended for use in the Cancer Drugs Fund will be funded in line with the terms of their managed access agreement, after the period of interim funding. The NHS England and NHS Improvement Cancer Drugs Fund list provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and

been launched in the UK.

4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance when the drug or treatment, or other technology, is approved for use within the Cancer Drugs Fund. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, for use within the Cancer Drugs Fund, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document or agreement of a managed access agreement by the NHS in Wales, whichever is the later.

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

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