

Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer

Technology appraisal guidance
Published: 13 May 2020

www.nice.org.uk/guidance/ta628

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1 Recommendations

1.1 Lorlatinib is recommended, within its marketing authorisation, as an option for treating anaplastic lymphoma kinase (ALK)-positive advanced non-small-cell lung cancer (NSCLC) in adults whose disease has progressed after:

- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor or
- crizotinib and at least 1 other ALK tyrosine kinase inhibitor.

It is recommended only if the company provides lorlatinib according to the [commercial arrangement](#).

Why the committee made these recommendations

Advanced ALK-positive NSCLC is usually first treated with an ALK tyrosine kinase inhibitor (alectinib or ceritinib, or crizotinib followed by either brigatinib or ceritinib). People then have either platinum doublet chemotherapy (PDC) or atezolizumab with bevacizumab, carboplatin and paclitaxel (ABCP).

Lorlatinib, another ALK tyrosine kinase inhibitor, has not been compared directly with other drugs. But analyses indirectly comparing lorlatinib with PDC and ABCP suggest that people who take lorlatinib:

- have longer before their disease progresses and may live longer than people who take PDC
- have longer before their disease progresses and may live longer than people who take ABCP.

Lorlatinib meets NICE's criteria to be considered a life-extending treatment at the end of life. Although the methods and results of the cost-effectiveness modelling are uncertain, the most likely cost-effectiveness estimates are within what NICE normally considers an acceptable use of NHS resources. Therefore, lorlatinib is recommended.

2 Information about lorlatinib

Marketing authorisation indication

- 2.1 Lorlatinib (Lorviqua, Pfizer) as monotherapy is indicated for 'the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) whose disease has progressed after:
- alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy; or
 - crizotinib and at least one other ALK TKI'.

Dosage in the marketing authorisation

- 2.2 The recommended dose is 100 mg lorlatinib taken orally once daily. Treatment with lorlatinib is recommended as long as the patient is benefitting from therapy without unacceptable toxicity.

Price

- 2.3 The list price of lorlatinib is £7,044.00 per 120-tablet pack of 25-mg tablets, and £5,283.00 per 30-tablet pack of 100-mg tablets (excluding VAT; BNF online accessed January 2020). The company has a [commercial arrangement](#). This makes lorlatinib 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](#) considered evidence submitted by Pfizer, a review of this submission by the evidence review group (ERG), and the technical report developed through engagement with 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:

- Including atezolizumab with bevacizumab, carboplatin and paclitaxel (ABCP) as a comparator in the appraisal was appropriate (issue 1, see technical report page 16).
- A hazard ratio of 0.8 was a reasonable estimate of the comparative efficacy between platinum doublet chemotherapy (PDC) and singlet chemotherapy (issue 2, see technical report page 18).
- Of the 6 proposed methods for indirect comparison with PDC, methods 3, 4 and 6 were dismissed by the company and ERG, leaving methods 1, 2 and 5 for committee consideration (issue 3, see technical report page 22).
- The generalised gamma curve was the most appropriate for measuring overall survival on lorlatinib (issue 4, see technical report page 26).
- Lorlatinib treatment for 3.5 months after progression was appropriate (issue 6, see technical report page 33).

- The revised assumptions for subsequent treatment discussed at the technical engagement stage were appropriate:
 - After lorlatinib: 45% of patients have subsequent treatments and the remaining 55% have best supportive care. Of the 45%, 66% have ABCP and 33% have PDC.
 - After PDC: 45% of patients have subsequent treatments and the remaining 55% have best supportive care. The 45% have immunotherapies in the proportions in the original company submission (69% atezolizumab, 31% bevacizumab based on [NICE's technology appraisal guidance on atezolizumab in combination](#)).
 - After ABCP: 75% of patients have docetaxel and 25% have best supportive care (issue 7, see technical report page 35).
- The company was not making a case for lorlatinib as a candidate for the Cancer Drugs Fund. This was appropriate because the ongoing lorlatinib clinical trials would not provide the evidence needed to resolve the uncertainties in this appraisal (issue 8, see technical report page 37).

The committee recognised that there were remaining areas of uncertainty associated with the analyses presented and took these into account in its decision making. It discussed the following issues (issues 3 and 5; see technical report, pages 19 and 27), which were outstanding after the technical engagement stage.

Clinical need

A third-generation ALK TKI would offer significant benefit to patients

- 3.1 The patient expert explained that there was a significant unmet need for patients with anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC), even though 4 ALK tyrosine kinase inhibitor (TKI) treatments are available. The committee noted that neither crizotinib nor ceritinib are preferred for untreated disease since the availability of alectinib. Brigatinib has been approved for previously treated disease only after crizotinib. If alectinib's treatment effect wanes the only current option is chemotherapy. ALK TKI treatments are a significant improvement over chemotherapy. People can live relatively normally and do not need to go to hospital for treatment. They do not have distressing

symptoms associated with chemotherapy such as hair loss. The patient expert explained that lorlatinib may be better tolerated than other ALK TKIs, appearing to cause less fatigue and fewer sun sensitivity and gastrointestinal problems. The clinical experts confirmed that there was a high unmet need for patients with ALK-positive NSCLC, because there is no cure for metastatic disease. Also, more than 50% of patients with ALK-positive NSCLC develop brain metastases, associated with high morbidity and mortality. Lorlatinib's ability to reach the brain means that patients whose brain tumours respond to treatment may have improved quality of life, allowing them to return to their usual activities. First and second-generation ALK TKIs (alectinib, ceritinib, crizotinib and brigatinib) are associated with the development of drug resistant mutations, leading to disease progression. Brain metastases and drug resistant mutations limit the duration of disease control and benefit from current ALK TKIs. For patients to survive for longer, and to avoid the devastating consequences of brain metastases, effective treatment that can penetrate the brain and overcome ALK-resistance mutations is needed. The committee noted that lorlatinib would be another line of ALK TKI treatment before a patient has chemotherapy or chemoimmunotherapy. The committee agreed that there was an unmet clinical need in ALK-positive NSCLC and that a third-generation ALK TKI, such as lorlatinib, would significantly benefit patients.

Clinical management

Current treatments after ALK TKIs are not effective for brain metastases

- 3.2 Current treatment options after ALK TKIs are standard care PDC, ABCP or best supportive care. The clinical experts explained that there was weak evidence for PDC-based regimens for this patient population, with a relative lack of efficacy in patients with brain metastases. The clinical experts explained that ABCP also has poor brain penetration and was not available to patients in the NHS in England with symptomatically active brain or leptomeningeal (central nervous system) metastases, which are common in ALK-positive NSCLC. In the absence of a third-generation ALK TKI such as lorlatinib, ABCP is expected to be used more in people

without symptomatically active central nervous system metastases. The committee agreed that the evidence for the efficacy of current treatments after ALK TKIs was weak in ALK-positive NSCLC and it was unclear how much benefit they had in people with brain metastases.

Clinical evidence

The main clinical evidence comes from a single-arm study

3.3 The main clinical evidence for lorlatinib came from study 1001, a single-arm, open-label, multicentre phase 1 to 2 trial, done in 13 countries but not in the UK. This study investigated the effect of lorlatinib in adults with metastatic (stage 4) ALK-positive NSCLC. It comprised 7 cohorts with 5 (EXP-2, EXP-3A, EXP-3B, EXP-4, EXP-5) representing populations having a mix of ALK TKIs and chemotherapy regimens. The company presented evidence for the combined cohort EXP-3B:5 of 139 patients. This was the pooled cohort of patients from cohorts EXP-3B, EXP-4 and EXP-5 whose treatment history most closely resembled that of the patient population covered by the marketing authorisation. Cohort EXP-3B was made up of 28 patients who had had first-line treatment with alectinib or ceritinib, with or without prior chemotherapy. The clinical experts explained that most patients would have alectinib as first-line treatment in the NHS, meaning that this cohort was the closest match to the NHS population. Cohort EXP-4 was made up of 65 patients who had previous treatment with 2 ALK TKIs, with or without prior chemotherapy. Cohort EXP-5 consisted of 46 patients who had previous treatment with 3 or more ALK TKIs, with or without prior chemotherapy. The primary outcome of study 1001 was objective response rate. Secondary outcomes included overall survival and progression-free survival. The results showed an objective response rate of 40.3% (95% confidence interval [CI] 32.1 to 48.9) with lorlatinib. The results also showed a progression-free survival of 6.9 months (95% CI 5.4 to 8.2) and a median overall survival of 20.4 months (95% CI 16.1 to not reached).

Indirect treatment comparisons

The results of the indirect treatment comparisons are uncertain

3.4 The company did an unanchored matching-adjusted indirect comparison (MAIC; as recommended in the [NICE Decision Support Unit's technical support document 18](#)), to compare the single-arm trial data for lorlatinib with trial data for PDC. The company chose 4 variables for matching:

- Eastern Cooperative Oncology Group performance status (0 and 1 or more than 1)
- brain metastases (yes or no)
- family origin (Asian or non-Asian)
- sex (male or female).

The PDC data in the indirect comparisons were from the ALUR and ASCEND-5 trials (for progression-free survival) and the PROFILE 1001 and PROFILE 1005 trials (for overall survival). In the trials everyone had advanced or metastatic ALK-positive NSCLC:

- ALUR compared alectinib with chemotherapy after previous treatment with PDC and crizotinib.
- ASCEND-5 compared ceritinib with chemotherapy after previous treatment with PDC and crizotinib.
- PROFILE 1001 was a single-arm phase 1 trial of crizotinib.
- PROFILE 1005 was a single-arm phase 2 trial of crizotinib after failure of 1 or more lines of systemic treatment for locally advanced or metastatic disease.

The company explained that in addition to the MAIC it used 2 further approaches for the indirect treatment comparison, giving 6 methods in total:

- hazard ratios estimated using a MAIC with EXP-2:3A (method 1) and EXP-3B:5 (method 2)

- hazard ratios estimated using an unadjusted indirect comparison with EXP-2:3A (method 3) and EXP-3B:5 (method 4)

- direct estimation of progression-free and overall survival by fitting parametric curves to chemotherapy data from the clinical studies (method 5) and the same parametric curves with a population adjustment because the populations in these clinical studies had fewer prior treatments than the EXP-3B:5 cohort (method 6).

The committee noted that methods 3, 4 and 6 had been dismissed at the technical engagement stage. The company preferred method 5, mainly because of concerns about whether the assumption of proportional hazards held for the duration of the model with methods 1 and 2. But the company said that methods 1 and 2 were also plausible approaches. The ERG had concerns about methods 1, 2 and 5, but considered that they were all plausible, and agreed that method 5 was preferred as the least problematic option. The committee agreed with the ERG that all the proposed indirect comparison methods were highly uncertain, but disagreed that methods 1 and 2 were reliable because of how the company had done the MAIC. The committee agreed that the company's approach of weighting patients in cohorts EXP-2:3A and EXP-3B:5 to match the patient characteristics of the populations from the ALUR and ASCEND-5 and PROFILE 1001 and PROFILE 1005 trials was correct. But it was concerned about how the MAIC had been implemented. The committee noted that matching the 2 pooled cohorts (EXP-2:3A and EXP-3B:5) to the same chemotherapy arm trial populations should have resulted in very similar hazard ratios being generated. Presenting hazard ratios from the MAIC that were not similar (and which resulted in large ICER differences) for EXP-2:3A (method 1) compared with EXP-3B:5 (method 2) showed that the matching adjustments used in the MAIC had failed. This was likely to be because of insufficient covariates being matched. The committee would have preferred a sensitivity analysis around the choice of variables included in the MAIC. The results that used methods 1 and 2 were therefore unreliable and unsuitable for decision making. The committee further discussed the company's rationale for doing the MAIC with both pooled cohorts. In general, the committee felt that using cohort EXP-2:3A for matching with the chemotherapy arm populations was not appropriate because this pooled cohort had a different treatment history and considerably different baseline characteristics to cohort EXP-3B:5. The clinical experts confirmed that cohorts EXP-4 and EXP-5 had already had 2 or 3 lines of treatment and had considerably more brain metastases than cohort EXP-2:3A. But the committee acknowledged that, overall, this was much less important than its fundamental

concern that the results of the MAIC were unsuitable for decision making, leaving only method 5 for consideration. The committee also agreed that the results of method 5, the indirect treatment comparison from applying independent curves without population adjustment, were highly uncertain.

Clinical effectiveness evidence in the economic model

The evidence for the PDC arm of the economic model is uncertain

3.5 The clinical effectiveness data for the PDC arm of the economic model were from the ALUR and ASCEND-5 trials (for progression-free survival) and the PROFILE 1001 and PROFILE 1005 trials (for overall survival). The ERG emphasised its concerns about the quality and suitability of the trial data. This was because most patients in these studies had previously had PDC and crizotinib (closely matching the treatment history of cohort EXP-2:3A from study 1001). Also, the patients in the chemotherapy arms of these trials had singlet chemotherapy (pemetrexed or docetaxel) rather than PDC. The committee agreed with the ERG and clinical experts that the company's assumption of equivalent clinical efficacy between doublet and singlet chemotherapy was not supported by clinical evidence, and that doublet chemotherapy was expected to be somewhat more effective than singlet chemotherapy. The committee noted that adjusting the hazard ratio by 20% to 0.8 to account for the difference in clinical efficacy between PDC and singlet chemotherapy was agreed to be appropriate at the technical engagement stage. It concluded that the treatment history differences between the trial populations used for PDC efficacy in the model and those of cohort EXP-3B:5 from study 1001 meant that the clinical effectiveness evidence for the PDC arm of the model was uncertain.

Population adjustment for ABCP overall survival is appropriate

3.6 The IMpower150 trial (comparing ABCP with bevacizumab plus carboplatin plus paclitaxel in people with chemotherapy-naive non-squamous NSCLC) was used to create an unanchored, unadjusted comparison of ABCP with lorlatinib. A mixed subgroup including patients

with epidermal growth factor receptor (EGFR)-positive and ALK-positive NSCLC was the only evidence available on using ABCP in ALK-positive NSCLC. The company applied a population adjustment to reflect that most of the relevant subgroup from IMpower150 had EGFR-positive NSCLC (n=30) rather than ALK-positive disease (n=11). The company claimed that the prognosis for ALK-positive NSCLC was poorer than for EGFR-positive disease, so a failure to adjust would bias the results against lorlatinib. The committee heard that there was a lack of robust evidence to support the company's claim. To do the adjustment, the company used data from the IMPRESS study (comparing continued treatment with gefitinib plus chemotherapy with placebo plus chemotherapy after first-line gefitinib in people with EGFR-positive NSCLC). The company compared response to chemotherapy in patients with EGFR-positive disease (using the IMPRESS data) with response to chemotherapy in patients with ALK-positive NSCLC (using data from ALUR and ASCEND-5 for progression-free survival and from PROFILE 1001 and PROFILE 1005 for overall survival). This provided hazard ratios, which were then applied to the fitted log-logistic and exponential curves for the mixed cohort with EGFR-positive and ALK-positive disease to derive curves for a cohort with only ALK-positive disease. The ERG stated that there was not enough evidence to provide validity for the extent of this adjustment, which shifts both the progression-free survival and overall survival in favour of lorlatinib. With the 20% hazard ratio adjustment made to the PDC arm data after the technical engagement stage (see [section 3.5](#)), the ERG explained that the overall survival curve for ABCP was now almost identical to the curve for PDC in the model, and this lacked clinical plausibility. The company and experts agreed that ABCP would be expected to be more effective than PDC, especially in patients without brain metastases. To correct this, the ERG suggested reducing the company's log hazard ratio adjustment to the ABCP curve for overall survival by 25% to improve clinical plausibility relative to the overall survival curve for PDC. The exact hazard ratios were considered academic in confidence by the company and cannot be reported here. The committee agreed with the ERG that the company's log hazard ratio adjustment of the ABCP curve was uncertain and that the ERG's 25% reduction to this adjustment seemed more clinically plausible for ABCP overall survival relative to PDC overall survival in the model.

Overall survival

10-year survival in this population is uncertain

3.7 To derive long-term overall survival for lorlatinib, parametric curves were fitted to the lorlatinib overall survival data taken from the EXP-3B:5 cohort from study 1001. The exponential curve had the best statistical fit, but the generalised gamma curve was selected as a compromise between the exponential curve and the log-normal curve preferred by the company's clinical experts based on the 10-year survival predictions. The exact overall survival values were considered academic in confidence by the company and cannot be reported here. The clinical expert consulted by the ERG considered that 10% projected survival at 10 years would be too optimistic and 2% would be more plausible. The clinical experts at the meeting confirmed that predicting 10-year survival in small populations with a very high incidence of brain metastases was highly uncertain because of a lack of reliable evidence. The committee heard that, in the absence of biomarkers for disease progression, brain metastases were the most reliable predictor of survival in patients with advanced ALK-positive NSCLC, and these patients would be expected to survive only for a few months. The committee noted that 66.9% of the pooled cohort EXP-3B:5 from study 1001 and 80.4% of cohort EXP-5 (3 or more prior ALK TKI therapies with or without any number of prior chemotherapy regimens) had brain metastases at baseline. The clinical experts at the meeting agreed that 10% projected survival at 10 years for this population was too high, and that lower values would be more plausible. The committee noted that the incremental cost-effectiveness ratio (ICER) was sensitive to the choice of curve and that using the exponential curve substantially increased the base-case ICER for lorlatinib compared with PDC. It concluded that although the generalised gamma curve had been agreed at the technical engagement stage, projecting 10-year survival in this population remained highly uncertain and it would take this uncertainty into account in its decision making.

Utility values in the economic model

The committee prefers a utility of 0.65 for progression on treatment and 0.46 for progression off treatment in both arms

3.8 The company did a systematic literature review to identify relevant studies with published utility values for ALK-positive NSCLC. The study by Labbé et al. (2017) was the largest published source of NSCLC ALK-positive EQ-5D questionnaire utility values, and the company selected the value of 0.65 from the study for the progressed disease state in both arms. The ERG was concerned that this value was likely to represent the health state shortly after progression rather than the whole progressed period and was therefore too high. The committee recalled that the ERG preferred the values from Chouaid et al. (2013) for progressed disease after second-line treatment (0.59) and after third or fourth lines of treatment (0.46). The clinical experts said that the best evidence for quality of life in this population was the QUARTZ study (Mulvenna et al. 2016), which looked at the quality of life of patients after treatment for brain metastases that were unsuitable for resection or stereotactic radiotherapy. The average utility for patients ranged from 0.5 to less than 0.4. But the population in QUARTZ was considerably less well than the population in study 1001 and had higher levels of comorbidity. So they felt that the value of 0.46 was too low for progressed disease in this appraisal because some people will continue to have lorlatinib treatment after progression. The committee asked the clinical experts which of the 3 options were most clinically plausible:

- a progressed health state utility value of 0.59
- a value of 0.65 for lorlatinib patients in progression on treatment and 0.59 for progressed disease and off treatment in both arms

- a value of 0.65 for lorlatinib patients in progression on treatment and 0.46 for progressed disease and off treatment in both arms.

The committee heard that because the disease and how it affects people varies, both 0.46 and 0.59 were plausible as averages across the progressed disease and off-treatment health state. One clinical expert strongly supported a 2-part utility value for progressed disease, on the basis that disease progression does not immediately correspond to an increase in a patient's symptom burden. But they were uncertain whether the second value should be 0.59 or 0.46. The committee asked the clinical and patient experts how the utility level declines for patients after symptomatic progression to understand which value would better reflect the average utility in progression off treatment with lorlatinib. The clinical experts agreed that some people, particularly with brain metastases, can deteriorate very quickly to a low level of utility with a very high symptom burden. On balance, given that patients had previously had treatment with surgery (56.1%) and radiotherapy (68.3%) and had a very high incidence of brain metastases (66.9%), the committee concluded that the preferred utility values were 0.65 for lorlatinib patients in progression on treatment and 0.46 for patients who had progressed and were off treatment in both arms.

Results of the cost-effectiveness analysis

The committee has preferred assumptions for decision making

3.9 The committee's preferred assumptions for decision making for PDC were:

- lorlatinib treatment for 3.5 months after progression
- hazard ratio of 0.8 for the relative efficacy of PDC compared with singlet chemotherapy
- MAIC method 5

- progressed disease utility of 0.65 for lorlatinib patients on treatment and 0.46 for lorlatinib patients off treatment, in both arms.

For ABCP its preferred assumptions were:

- company's population adjustment of ABCP overall survival reduced by 25%
- lorlatinib treatment for 3.5 months after progression
- progressed disease utility of 0.65 for lorlatinib patients on treatment and 0.46 for lorlatinib patients off treatment, in both arms.

At consultation, the company submitted analyses that incorporated the committee's preferred assumptions and an updated commercial arrangement.

The range of most plausible cost-effectiveness estimates for lorlatinib is less than £50,000 per QALY gained

- 3.10 Because lorlatinib and the comparators have commercial arrangements, the exact ICERs are confidential and cannot be reported here. The committee noted that its preferred assumptions produced a range of deterministic ICERs for lorlatinib compared with PDC and ABCP which were less than £50,000 per quality-adjusted life year (QALY) gained.

End of life

Lorlatinib meets the criteria to be considered a life-extending, end-of-life treatment compared with PDC and ABCP

- 3.11 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](#). For PDC, average life expectancy was well below 2 years in the company's base case and remained under 2 years across the scenarios assessed. Despite the limitations in the comparative evidence base, it was plausible that lorlatinib treatment would result in a survival gain of more than 3 months compared with PDC. Although there was some uncertainty around the average life expectancy with ABCP treatment because of the population adjustment applied by the company

to the fitted curve, this was also expected to be less than 2 years. Also, life expectancy with ABCP remained under 2 years when the log hazard ratio for the population adjustment of overall survival was reduced by 25%, as agreed by the committee. The survival gains for lorlatinib compared with ABCP were more than 3 months across all scenarios assessed. The committee concluded that lorlatinib met the criteria to be considered a life-extending, end-of-life treatment when compared with both PDC and ABCP.

Innovation

The model adequately captures the benefits of lorlatinib

3.12 The company considered lorlatinib to be innovative, highlighting that it was a third-generation ALK TKI that penetrates the central nervous system and is retained in the intracranial space. So it potentially addresses the unmet need for additional treatment options for patients who develop brain metastases. It was specifically designed to inhibit resistant ALK mutations, including the ALKG1202R mutation that increases significantly after treatment with second-generation ALK TKIs. The clinical experts agreed that lorlatinib was an effective third-generation ALK TKI with good brain penetration and that people would welcome additional treatment options. The committee concluded that it had not been presented with any additional evidence of benefits that were not captured in the measurement of the QALYs and the resulting cost-effectiveness estimates.

Other factors

3.13 No equality or social value judgements were identified.

Conclusion

Lorlatinib is recommended for routine commissioning

3.14 The committee acknowledged the need for treatment options for people

with previously treated ALK-positive advanced NSCLC. Because the range of plausible ICERs was less than £50,000 per QALY gained, the committee concluded that lorlatinib can be considered cost effective. Therefore, it can be recommended for routine commissioning as an option for previously treated ALK-positive advanced NSCLC.

4 Implementation

- 4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 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 routine commissioning, 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. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or fast track appraisal), at which point funding will switch to routine commissioning budgets. 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 a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.
- 4.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has previously treated anaplastic lymphoma kinase-positive advanced non-small-cell lung cancer and the doctor responsible for their care thinks that lorlatinib is the right treatment, it should be available for use, in line with NICE's recommendations.

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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ISBN: 978-1-4731-3774-5

Accreditation

