Lorlatinib for previously treated ALK-positive advanced non-small-cell lung cancer [ID1338]

Produced by Aberdeen HTA Group

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Contribution of authors

Graham Scotland, Andrew Walker and Daniel Kopasker acted as health economists for this appraisal: critiqued the cost-effectiveness evidence, checked the economic model, and conducted further sensitivity analyses. Shona Fielding with help from Thenmalar Vadiveloo acted as lead statistician for this appraisal: critiqued the statistical methods presented in the submission, checked the numerical results, analyses, tables, and figures related to the review of the clinical effectiveness evidence. Clare Robertson acted as systematic reviewer: critiqued the company's definition of the decision problem, the clinical effectiveness evidence and the methods used for identifying relevant studies. Paul Mason acted as information scientist: critiqued the methods used for identifying relevant studies and checked the search strategies presented in the submission. Gillian Price acted as clinical advisor: provided clinical advice and general guidance. Miriam Brazzelli led the clinical effectiveness side of the appraisal. Graham Scotland acted as project lead and led the cost-

effectiveness side of the appraisal. All authors contributed to the writing of this report and approved its final version.

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List of abbreviations

ALK	Anaplastic lymphoma kinase
NSCLC	Non-small cell lung cancer
TKI	Tyrosine kinase inhibitor
QoL	Quality of life
ERG	Evidence review group
CS	Company submission
PDC	Pemetrexed with cisplatin/carboplatin
ABCP	Atezolizumab with bevacizumab, paclitaxel and carboplatin
MAIC	Matched adjusted indirect comparison
RCT	Randomised controlled trial
CRD	Centre for reviews and dissemination
ORR	Objective response rate
IC-ORR	Intercranial objective response rate
BOR	Best observed response rate
TTR	Time to tumour response
IC-TTR	Intercranial time to tumour response
DOR	Duration of response
DCR	Disease control rate
PFS	Progression free survival
OS	Overall survival
OD	Once daily
AE	Adverse event
EGFR	Epithelial growth factor receptor
ECOG	Eastern Cooperative Oncology Group
HR	Hazard ratio
CI	Confidence interval

1 Summary

1.1 Critique of the decision problem in the company submission

The population addressed in the company submission is people with advanced ALK-positive NSCLC that have progressed after treatment with one or two ALK-TKIs with or without prior chemotherapy. The intervention is lorlatinib, a selective adenosine triphosphate competitive inhibitor of ALD and c-ros oncogene 1 tyrosine kinases for the treatment of adult patients whose disease has progressed after first line alectinib or ceritinib ALK TKI therapy or crizotinib and at least one other ALK TKI. Contrary to the NICE final scope, the comparator addressed in the CS is limited to pemetrexed with cisplatin/carboplatin (PDC). The company did not consider atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP) a relevant comparator, but at the request of NICE did provide an update which included ABCP in the economic model. The ERG considers ABCP a relevant comparator.

1.2 Summary of clinical effectiveness evidence submitted by the company

The clinical effectiveness evidence for lorlatinib submitted by the company relates to a single phase two study, Study 1001[1]. This study investigates the single arm of lorlatinib for adult patients with metastatic (stage IV) ALK-positive NSCLC. The evidence presented is for the combined cohort EXP-3B:5 and consists of 139 patients. The company presented evidence that shows lorlatinib to be effective for their primary outcome, objective response rate (40.3% with 95% CI 32.1-48.9), and also showed positive results for their secondary outcomes (see section 4.2) including progression free survival of 6.9 months (95% CI 5.4-8.2).

1.3 Summary of the ERG's critique of clinical effectiveness evidence submitted

The comparator evidence was limited to chemotherapy and the company did not consider ABCP relevant. The chemotherapy evidence was provided by three studies ALUR[2] and ASCEND5[3] (progression free survival) and PROFILE 1001/1005[4] (overall survival). The company used a matched adjusted indirect comparison to provide hazard ratios for lorlatinib versus chemotherapy for these outcomes. This

analysis showed a survival benefit (both progression free and overall) for patients treated with lorlatinib versus chemotherapy.

The ERG has reservations over the clinical effectiveness evidence submitted for the following reasons:

- evidence base for lorlatinib is from a single study, of one arm, in only 139 patients
- company indicate chemotherapy (PDC) as the only relevant comparator and did not fully consider ABCP
- evidence base for chemotherapy comes from 3 studies, which have different prior treatment pathways to the target population for lorlatinib
- there is an assumption by the company that PDC, pemetrexed monotherapy and docetaxel monotherapy are equivalent and the ERG's opinion is that PDC is superior. Pemetrexed and docetaxel were the chemotherapies used in these studies as all participants within ALUR, ASCEND5 and PROFILE 1001/1005 had previously been treated with PDC. The company offered a counter argument that patients in these trials were exposed to only one ALK TKI (crizotinib), whereas the population eligible for lorlatinib may have been exposed to two or more and so might be expected to have a worse efficacy outcome (as suggested by some clinical experts). However, the ERG remains concerned about the potential for underestimating the efficacy of PDC.
- choice of studies to inform the MAIC may not be appropriate for the reasons stated above
- the company did not use the results of the MAIC in the base case of the economic model

1.4 Summary of cost effectiveness submitted evidence by the company

The company submitted a de novo cost-effectiveness model comparing lorlatinib to PDC in people with advanced ALK-positive NSCLC that have progressed after treatment with one or two ALK-TKIs. A further comparison was provided against ABCP, originally as an addendum, but later as an appendix to the CS. This later comparison was only provided as a deterministic analysis.

The company used as partitioned survival model with three health states: progression free, progressed and dead. PFS and OS for lorlatinib were informed by fitting

parametric distributions to Study 1001 efficacy data. As Study 1001 was a single arm trial, the company derived comparative effectiveness data for PDC by indirect comparison with other data sources: The chemotherapy arms of ALUR and ASCEND-5 for PFS and a retrospective analysis of the chemotherapy arms of the chemotherapy arms of PROFILE 1001/1005 for OS. The company explored six different methods for deriving comparative PFS and OS data, including the estimation of hazard ratios from MAICs and unadjusted comparisons, and independent curve fitting with and without population adjustment to account for differences in the ALK INH treatment histories between the comparator studies (post-crizotinib) and the population of relevance for lorlatinib (post-second generation ALK INH). The company ultimately selected independent curves without population adjustment (method 5) for their base case. This was due to concerns regarding the proportional hazard assumption required for the application of hazard ratios, and advice from clinical experts that PDC would be expected to perform equally poorly following treatment with crizotinib or a second-generation ALK TKI.

For the comparative efficacy of ABCP, the company used data from a mixed ALK+/EGFR+ subgroup from the IMPower study. Independent curves were fitted to the observed PFS and OS Kaplan Meier data, but a population adjustment was undertaken to account for poorer expected outcomes for a pure ALK+ cohort.

Treatment specific EQ-5D health state utility values (HSUVs) were applied in the progression free state of the model, and a single HSUV (0.65) was applied to the progressed state. The lorlatinib progression free HSUV ([redacted]) was derived by mapping from EORTC QLQ-C30 data collected in Study 1001. The corresponding HSUV for the PDC arm (0.72) was identified by review of the literature, and for the ABCP comparison a value of 0.71 was taken from an analysis conducted by the ERG in TA584. It was assumed that the treatment specific progression free utilities captured the impact of adverse events, but a scenario that explicitly incorporated QALY decrements associated with adverse events was also provided for the PDC comparison.

The model incorporated treatment acquisition costs, administration costs, adverse event costs, other health state costs, subsequent treatment costs, and end of life costs.

The CS recognised that treatment with lorlatinib can continue beyond progression, and so explored the use of different parametric curves for modelling time on treatment. However, due to inconsistencies with the selected PFS curve, these were rejected by the company in their base case. Instead they applied an average of [redacted] months on treatment following progression, which was the difference between restricted mean time on treatment and restricted mean PFS up to a time point of [redacted] months. For PDC it was assumed that it would be administered for a maximum of six cycles or until progression. Thereafter, 100% of those remaining progression free were assumed to proceed with pemetrexed maintenance. For ABCP, time on treatment was equated to PFS, but a stopping rule was applied at two-years (i.e. all patients removed from treatment from two years).

With respect to subsequent treatment, 60% of progressed patients were assumed to proceed with a subsequent active therapy in all arms of the model. For subsequently treated patient the distributions were: 60% PDC and 40% pemetrexed monotherapy following lorlatinib; 69% pembrolizumab and 31% atezolizumab following PCD; and 100% docetaxel following ABCP. Since the company did not have access to confidential discount prices for atezolizumab, pembrolizumab or bevacizumab, they assumed a 30% discount in their analyses to avoid overestimating costs. The ERG has rerun the company's analyses in a confidential comparator PAS appendix using the actual PAS discounts available to the NHS.

1.5 Summary of the ERG's critique of cost effectiveness evidence submitted

The ERG notes the following main areas of concern with the company's economic evidence:

1. The design of Study 1001, as a non-comparative single-arm study, means there is substantial uncertainty in estimating the lifetime comparative effectiveness of lorlatinib in its licensed indication. While the company has undertaken an indirect comparison to address this, there are several issues and much uncertainty remains. Issues include:

- The selection of clinical studies to represent the PDC treatment arm, these being representative of pemetrexed or docetaxel monotherapy, or undefined systemic therapy rather than PDC.

- The selection of the method to carry out the indirect comparison, with the adjusted HRs from the MAIC being rejected in favour of independently fitted curves without adjustment.
- The source of data and approach to applying the EGFR+ to ALK+ population adjustment in the ABCP comparison:
    - The population adjustment hazard ratios were derived from unadjusted indirect comparison of study arms that differed in the type of chemotherapy received and not just the population.
    - The adjustment hazard ratios were applied to ABCP curves derived from a mixed cohort (27% ALK+) rather than a pure EGFR population.

2. The utility values selected are open to challenge:
    - The value for the progressed disease state may be on the high side compared to other available published studies.
    - There is no direct comparative evidence that pre-progression utility on lorlatinib is higher than pre-progression utility on PDC or later pemetrexed maintenance. The same point applies in the comparison with ABCP.

3. The treatment duration calculation for lorlatinib is based on the difference between the restricted mean ToT and PFS at 27.2 months in Study1001. The ERGs clinical expert advised that this might underestimate the extent by which clinicians tend to prolong treatment in routine clinical practice when there are no other effective options available.

4. The assumption that an equal proportion of patients receive subsequent therapy irrespective of previous treatment is open to question. In addition, the distribution of subsequent therapies in each arm of the model is uncertain.

1.6 ERG commentary on the robustness of evidence submitted by the company

1.6.1 Strengths

Study 1001 provides a reasonable source of data for modelling expected progression-free and overall survival expectations for the relevant population of lorlatinib treated patients.

1.6.2 Weaknesses and areas of uncertainty

The key area of uncertainty with respect to the clinical and cost effectiveness evidence relates to the single arm study design of Study 1001, which necessitates the use of matched adjusted or unadjusted indirect comparisons. Uncertainty surrounding the comparative effectiveness of PDC and ABCP is further increased by the reliance on data that does not ideally reflect the treatment comparators and/or the population in the scope.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted several further deterministic exploratory scenario analyses, which identified the following insights:

- The ICER for lorlatinib versus PDC ranges from £43,799 (method 6) to £58,747 (method 2) when the alternative methods for estimating comparator effectiveness are applied to both OS and PFS at the same time. Method two may be a reasonable alternative to the company base case although it relies on the proportional hazards assumption.
- The ICER versus PDC rises to £55,638 if the hazard of progression and death on PDC is 40% lower than in the chemotherapy arms of the studies used inform these outcomes in the company's model.
- The ICER versus PDC is quite sensitive to the average post progression time on treatment with lorlatinib; rising to £53,938 if this is increased to [redacted] and £59,496 if this is [redacted]. An alternative approach of using the generalised gamma curve to model ToT resulted in an ICER of £56,876.
- If subsequent treatment with pembrolizumab following progression on PDC is costed at the fixed dose of 200mg every two weeks, the company base case ICER drops to £48,288.
- Changing assumptions about the proportion of patients who receive further treatment following PDC, or the distribution between PDC and pemetrexed monotherapy following lorlatinib, had little impact on the ICER.

With respect to the ABCP comparison:

- The ICER for lorlatinib was moderately sensitive to the post progression time on treatment for lorlatinib, but otherwise remained below £30,000 in the scenarios assessed by the ERG.
- Of note, when reducing the population adjustment for the increased hazard of progression and mortality in ALK+ versus EGFR+ patients, the ICER for lorlatinib dropped initially when applying a 25% reduction in the adjustment log HRs and only rose slightly when there was a 50% reduction.

Uncertainties surrounding progressed disease utility value applied in the company model also results in upward uncertainty in the ICER versus PDC and ABCP. All summarised findings above reflect analyses where drug prices are set as per the company base case. The results of the ERGs exploratory analyses are provided with current comparator PAS discounts in a confidential appendix.

2 Background

2.1 Critique of company's description of underlying health problems

The relevant health condition for this submission is anaplastic lymphoma kinase (ALK) positive non-small cell lung cancer (NSCLC). The company's description of ALK-positive NSCLC in terms of prevalence, symptoms and complications appears generally accurate and appropriate to the decision problem.

Over 39,000 new cases of lung cancer were diagnosed in England and Wales in 2016[5]. NSCLC accounts for 88.5% of all lung cancer cases[5]. ALK-positive NSCLC is a subset of NSCLC, with estimated prevalence rates of between 1.6% and 5%[6-11] and is associated with advanced clinical stage and presentation[12, 13]. ALK-positive patients experience a high symptom burden, including fatigue, dyspnoea, cough, pain, weight loss, depression, shortness of breath and haemoptysis[14, 15]. The brain is a common site for progression, particularly in patients with a history of prior ALK tyrosine kinase inhibitor (TKI) treatment (45-70% of patients)[16]. Brain metastases can result in neurological dysfunction, cognitive impairment and are associated with poor prognosis[16]. ALK-positive NSCLC tend to be of younger age[12, 17] and are therefore more likely to be of working age, have dependents or be carers than those with ALK-negative disease. ALK-positive disease, therefore, has a particularly high impact on quality of life (QoL) and productivity loss.

2.2 Critique of company's overview of current service provision

The ERG considers the company's description of current service provision is accurate. ALK TKI treatments are approved as first and second line therapies. The company presents those treatments that are currently available in the UK, and the associated NICE treatment guidelines in Tables 4 and 5, Document B, of the CS and these are reproduced by the ERG below.

Table 1 ALK TKIs currently approved for the treatment of ALK-positive NSCLC in the UK

Generation	Name	Indication
First	Crizotinib (Xalkori®)	Crizotinib as monotherapy is indicated for: The first-line treatment of adults with ALK-positive advanced NSCLC The treatment of adults with previously treated ALK-positive advanced NSCLC The treatment of adults with ROS1-positive advanced NSCLC.[18]
Second	Ceritinib (Zykadia®)	Ceritinib as monotherapy is indicated for: The first-line treatment of adult patients with ALK-positive advanced NSCLC The treatment of adult patients with ALK-positive advanced NSCLC, previously treated with crizotinib.[19]
	Alectinib (Alecensa®)	Alectinib as monotherapy is indicated for: The first-line treatment of adult patients with ALK-positive advanced NSCLC The treatment of adult patients with ALK-positive advanced NSCLC, previously treated with crizotinib.[20]
	Brigatinib (Alunbrig®)	Brigatinib is indicated as monotherapy for the treatment of adult patients with ALK-positive NSCLC previously treated with crizotinib.[21]

ALK = anaplastic lymphoma kinase; NSCLC = non-small cell lung cancer; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor; UK = United Kingdom

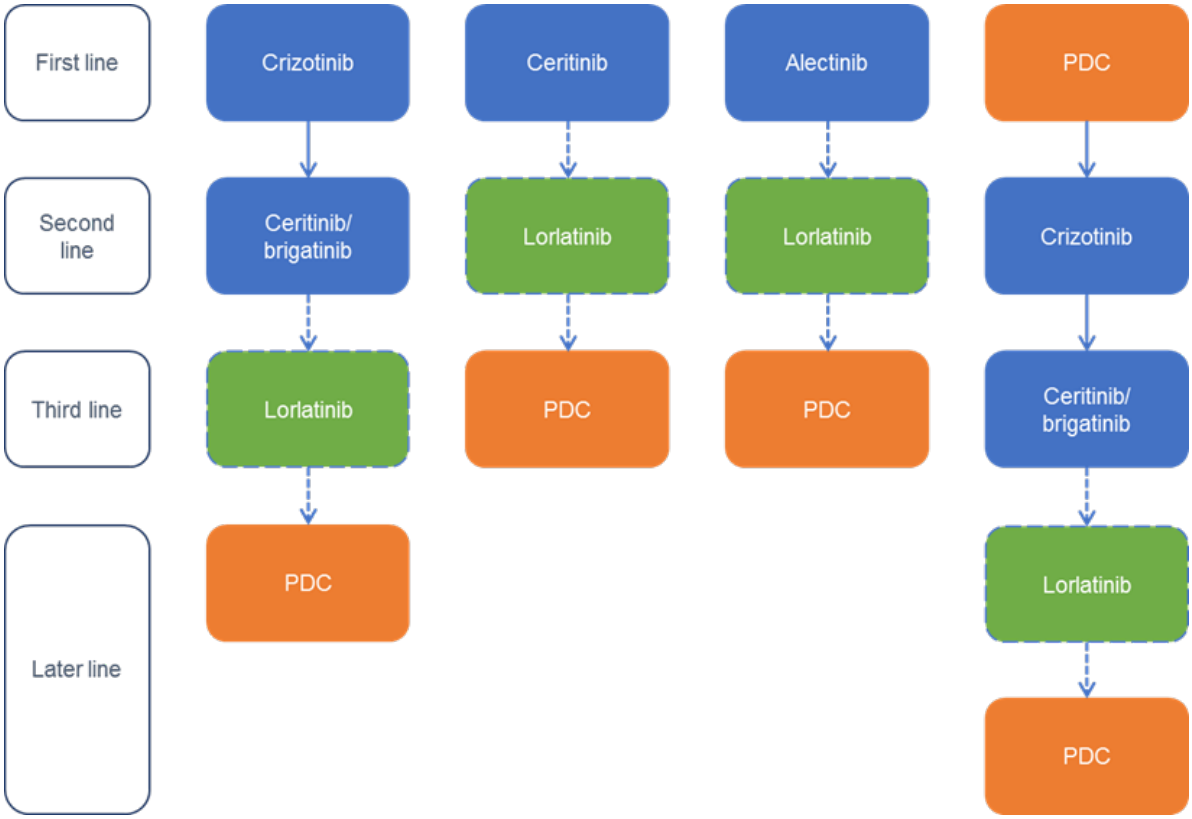
Table 2 Current NICE guidelines for the treatment of advanced ALK-positive NSCLC

Treatment line	Recommendation
First	PDC (patients with Stage III or IV NSCLC and good PS) or single-agent chemotherapy for patients who are unable to tolerate a platinum combination[22] Crizotinib[23] Ceritinib[24] Alectinib[25]
Second	Chemotherapy[22] Crizotinib[26] Ceritinib, if previously treated with crizotinib[27] Brigatinib, if previously treated with crizotinib[21]

ALK = anaplastic lymphoma kinase; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy; PS = performance status

Crizotinib, ceritinib, alectinib and brigatinib are currently recommended for the treatment of ALK-positive NSCLC by both NICE and the European Society for Medical Oncology (ESMO)[21, 23-28]. The company notes that, while second-generation ALK TKIs offer the opportunity to sequence multiple targeted therapies, data are limited. The ERG agrees with the company that for certain lines of ALK-positive NSCLC treatment the current data are limited. The ERG clinical expert believes that all patients will have routine ALK testing at diagnosis. The ERG clinical expert agrees with the company that maximising the time patients are treated with targeted ALK TKIs to delay the need for chemotherapy is an aim of treatment and that lorlatinib will always be given after other ALK TKIs. The company state that lorlatinib will extend the possible treatment time with targeted ALK TKIs. The company present the proposed treatment pathways following the introduction of lorlatinib in Figure 2, Document B, of the CS and this is reproduced by the ERG below. It is the ERG clinical expert's opinion that alectinib is the first line treatment for most patients as it performs better that crizotinib and has a better toxicity profile compared with ceritinib. The ERG clinical expert agrees with the company's statement that clinical opinion suggests that the pathway beginning with alectinib will become the standardised pathway for up to 90% of ALK-positive NSCLC patients in the near future; and that the pathway beginning with crizotinib represents a small patient pool that is likely to shrink further. It is worth noting that the clinical pathway proposed initially by the company and reproduced here as Figure 1 does not

include atezolizumab plus bevacizumab, paclitaxel and carboplatin (ACBP), which is now recommended by NICE (TA584)[29] as an option for ALK-positive NSCLC.



ALK = anaplastic lymphoma kinase; NICE = National Institute for Health and Care Excellence; NSCLC = non-small cell lung cancer; PDC = platinum doublet chemotherapy

Figure 1 Treatment pathways for patients with ALK-positive NSCLC, based on licensed indications and current NICE guidance, following the introduction of lorlatinib

3 Critique of company's definition of decision problem

3.1 Population

The population addressed in the NICE final scope and the CS is people with advanced ALK-positive NSCLC that have progressed after treatment with alectinib or ceritinib as the first ALK TKI or progressed after treatment with crizotinib and at least one other ALK TKI.

3.2 Intervention

The intervention in both the NICE final scope and the CS is lorlatinib. The company provides details of the technology in the draft summary of product characteristics in Appendix C of the company submission (CS) and a summary in Table 2, Document B, of the CS. Briefly, lorlatinib is a selective adenosine triphosphate competitive inhibitor of ALD and c-ros oncogene 1 tyrosine kinases and is intended as monotherapy in the treatment of adults patients whose disease has progressed after first line alectinib or ceritinib ALK TKI therapy or crizotinib and at least one other ALK TKI.[30] The recommended dose of lorlatinib is 100mg taken orally, as a tablet, once daily. Due to limited data, no dose recommendation is available for patients aged 65 years and older.[31] Lorlatinib is contraindicated or not recommended in patients who are hypersensitive to lorlatinib, or any of the excipients, taking strong CYP3A4/5 inducers, pregnant or breast-feeding during and for seven days after the last treatment dose.[31] Avoidance of pregnancy during lorlatinib treatment is advised as studies in animals have shown embryo foetal toxicity. Lorlatinib can render hormonal contraceptives ineffective. Condoms should be used either alone or in combination with hormonal contraceptives during treatment and for at least 14 weeks after the final dose. Male fertility may be compromised during treatment[31] and advice on effective fertility preservation should be sought before treatment commences. Whether lorlatinib affects female fertility is currently unknown.[31] Lorlatinib received conditional approval in the EU for the population indicated in the CS on 7th May 2019.

3.3 Comparators

The comparators in the NICE final scope are:

For people who have not had previous chemotherapy:

- Pemetrexed with cisplatin/carboplatin (adenocarcinoma or large cell carcinoma only)
    - with or without pemetrexed maintenance
- Atezolizumab with bevacizumab, paclitaxel and carboplatin (non-squamous only) [subject to NICE appraisal].

For people who have had previous chemotherapy (but not a PD-L1 immunotherapy):

- Atezolizumab (for adults with locally advanced or metastatic NSCLC who have previously received chemotherapy and targeted ALK treatment)
- Pembrolizumab (for adults with locally advanced or metastatic PD-L1-NSCLC who have had at least one chemotherapy and targeted ALK treatment)
- Best supportive care.

For people who have had previous treatment with an immunotherapy (PD-L1 inhibitor):

- Nintedanib with docetaxel (adenocarcinoma only)
- Docetaxel
- Best supportive care.

The comparator addressed in the CS is limited to pemetrexed with cisplatin/carboplatin (PDC). The company outline their rationale for differing in the choice of comparators outlined in the NICE final scope in Table 1, Document B, of the CS. The company state in their decision problem that PDC is the standard of care comparator for the vast majority of indicated patients. The company also state that they do not propose making a comparison based on whether patients have or have not received prior chemotherapy, arguing that few patients will have received chemotherapy, and these patients would not receive lorlatinib until the fourth line according to the NICE care pathway and, therefore, represent such a small fraction of the total population that does not warrant a standard of care comparison. The company further state that patients who receive chemotherapy post ALK TKI are a temporary population as no further ALK TKIs are currently available. The company

argue that recommendation of lorlatinib would render the chemotherapy post ALK TKI population obsolete. The company also suggest that lorlatinib should be considered for use after a second-generation ALK TKI in line with EMA marketing authorisation, which does not restrict lorlatinib based on prior chemotherapy status. The ERG clinical expert agrees with the company that lorlatinib will be given as second-line therapy after other ALK TKIs, unless people who have received crizotinib first-line, in which case brigatinib (instead of ceritinib) would be the more usual second-line therapy due to its more favourable safety profile.

The company state that best supportive care cannot be a comparator in this appraisal because patients receive this when they cannot tolerate or respond to ALK-inhibitors or PDC and argue that the remaining treatments, which are used conditionally based on previous immunotherapy, also cannot be comparators as very few patients have immunotherapies in any line. The company cite evidence from the UK ALK-positive database in reference to this assertion.[32]

The company state that they do not consider atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP) to be a relevant comparator for this submission based on the fitness of ALK-positive NSCLC patients and the high proportion with brain metastases, low expected uptake of ABCP in these patients due to no precedent of use and lack of powered clinical evidence and advice from expert oncologists who suggested that ABCP would predominantly be used in epidermal growth factor receptor (EGFR) patients. It is the ERG clinical expert's opinion that ABCP is a relevant comparator for lorlatinib. ALK-positive patients are likely to be generally fit compared with other NSCLC patients; however, their status is likely to deteriorate quickly following relapse on targeted therapies. ABCP use is likely to increase as standard care following targeted therapy as it allows immunotherapy to be moved up one line for those patients who are likely to benefit from this therapy. Following a request from NICE, the company incorporated ABCP as comparator in the company's economic model.

3.4 Outcomes

The outcomes stated in both the NICE final scope and CS are: overall survival (OS), progression free survival (PFS) response rates (including intercranial response), adverse events (AEs) and health-related quality of life (HRQoL).

3.5 Other relevant factors

The ERG agrees with the company that there are no known equality issues relating to the use of lorlatinib in patients with ALK-positive NSCLC.

4 Clinical effectiveness

4.1 Critique of the methods of review(s)

4.1.1 Searches

Appendix D in the CS provides details of the searches that were undertaken to identify studies included in the reviews of efficacy and safety. The major relevant databases searched were: Embase and MEDLINE (using Embase.com), MEDLINE In-Process (using Pubmed.com) and the Cochrane Library (including the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, Cochrane Central Register of Controlled Trials, and the Health Technology Assessment Database). No date limit was applied to the original search, which was updated in April 2019. In addition, the company searched proceedings of several relevant conferences and websites. Handsearching of bibliographies of key systematic reviews and meta-analyses were also screened.

The search strategies are documented in full in Appendix D of the CS. The company used Embase.com to search the incorporated Medline records as well as Embase content. This can lead to records being missed due to the automated conversion of MeSH terms to Emtree. However, the combination of index terms, text words, and drug identifiers in the search strategy has produced a highly sensitive search. The searches are fully reproducible and the range of sources searched is comprehensive and appropriate. The search will have identified all the relevant literature.

4.1.2 Inclusion criteria

The company provides details of the systematic review inclusion and exclusion criteria in Table 12, Appendix D, of the CS. Primary screening of titles and abstracts and secondary screening of full text articles were conducted independently by two reviewers. A third independent reviewer checked any uncertainty regarding the inclusion of studies. The ERG considers these methods comprehensive and appropriate.

The company provide the PRISMA flow diagram[33] of studies identified by their systematic review as Figure 1 in Appendix D of the CS. The company identified six RCTs, from 61 articles, and 87 non-RCT studies, from 238 articles, as eligible for inclusion in their review. Details of the included studies are presented in Table 13 in Appendix D. At clarification the company further explained that although six RCTs and 87 non-RCTs were identified as eligible, no other trial other than Study 1001[1], assessed lorlatinib as an intervention. The company state that Study 1001 is, therefore, the only trial that is relevant for this appraisal. Even though specific reasons for the exclusion of the eligible RCTs and non-RCTs were not provided by the company in their submission, the ERG agree that Study 1001 is the main source of evidence for the assessment of lorlatinib and it is unlikely that other relevant lorlatinib studies had been omitted.

4.1.3 Critique of data extraction

One reviewer conducted data extraction using a pre-agreed data extraction template. Extracted data were then independently checked for errors by a second reviewer. The ERG considers the data extraction methods used for the clinical effectiveness review robust.

4.1.4 Quality assessment

The company provide details of the quality assessment of the included RCTs and non-RCTs in Tables 27 and 28 in Appendix D of the CS. The company assessed Study 1001 using the Downs and Black checklist.[34] The ERG considers the company's quality assessment methods appropriate.

The ERG conducted a quality assessment of the methods used by the company for the systematic review of clinical evidence using the Centre for Review and Dissemination (CRD) criteria. Results are presented in Table 3.

Table 3 Quality assessment of the company's systematic review of clinical effectiveness evidence

CRD quality item	Yes/No/Unclear
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes
2. Is there evidence of a substantial effort to search for all of the relevant research?	Yes
3. Is the validity of included studies adequately assessed?	Yes
4. Are sufficient details of the individual studies presented?	Yes
5. Are the primary studies summarised appropriately?	Yes

4.1.5 Evidence synthesis

The clinical effectiveness evidence for lorlatinib submitted by the company relates to a single phase two study, Study 1001[1]. This study is single arm investigating lorlatinib as a single agent in adult patients with metastatic (stage IV) ALK-positive NSCLC and consists of several cohorts of patients. The clinical effectiveness evidence is based upon the pooled EXP-3B:5 cohort (Table 4) and consists of 139 patients (data cut 2 February 2018). According to the opinion of the ERG's clinical expert, EXP-3B represents the typical cohort of patients that would receive lorlatinib in current clinical practice. However, due to the historical clinical pathway of recent years, EXP-4 and EXP-5 are also relevant, so the ERG agrees that pooling data from EXP-3B, EXP-4 and EXP-5 (EXP-3B:5) is acceptable. Patients in the EXP-2 and EXP-3A cohorts have received crizotinib as first line treatment; however, this is no longer considered a standard care pathway. So, the ERG agrees with the company that these cohorts are not relevant for this technology assessment.

Table 4 Study 1001 EXP cohorts

ALK/ROS 1 status	Cohort	Prior treatment regimen
ALK-positive	EXP-1	Treatment-naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ALK TKI therapy)
	EXP-2	Patients relapsing after crizotinib therapy only
	EXP-3A	Patients relapsing after crizotinib therapy and one or two prior regimens of chemotherapy
	EXP-3B	Patients relapsing after one ALK TKI therapy other than crizotinib with or without any number of prior chemotherapy regimens
	EXP-4	Patients relapsing after two prior ALK TKI therapies with or without any number of prior chemotherapy regimens
	EXP-5	Patients relapsing after three or more prior ALK TKI therapies with or without any number of prior chemotherapy regimens
ROS1-positive	EXP-6	Treatment naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ROS1 inhibitor therapy) or patients who had any number of prior cancer therapies (chemotherapy and/or ROS1 inhibitor therapies)

Abbreviations: ALK = anaplastic lymphoma kinase; EXP = expansion; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor

Source: Company Submission, Document B, Table 8.

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The primary efficacy outcome in Study 1001 is the objective response rate (ORR) and intracranial objective response rate (IC-ORR). Secondary outcomes include time to tumour response, duration of response, disease control rate, time to tumour progression, progression free survival and overall survival. Patient reported outcomes were assessed using the EORTC QLQ-C30 and the corresponding lung cancer module QLQ-LC13.

The company present the baseline characteristics of the patients in Study 1001 in Table 11, Document B, CS, and present them separately for the cohorts EXP-3B, EXP-4, EXP-5 and well as for the pooled EXP-3B:5. In summary in the pooled cohort (n = 139), mean (SD) age was 52.5 (11.6), 43.9% male, 47.5% white, 38.1% Asian,

43.5% ECOG PS = 0 and 52.2% ECOG PS = 1, with 66.9% having brain metastases. The ERG note that the three cohorts were comparable for age, gender and ECOG PS, but EXP-3B had far fewer white participants [25% versus 49.2% (EXP-4) and 58.7% (EXP-5)] and a higher proportion of Asians (57.1% versus 35.4% and 30.4%, respectively). The proportion of patients with brain metastases at baseline was higher in EXP-5 (80.4%) than in both EXP-3B (42.9%) and EXP-4 (67.7%). The company reported that in the pooled cohort, the median duration of treatment was 10.1 months, range 0.2-27.9 months. The ERG considers the pooled EXP-3B:5 cohort appropriate and agree that the patient characteristics are broadly similar and representative of the target population.

4.2.1 Primary outcome: objective response rate (ORR) and intracranial objective response rate (IC-ORR)

Objective response rate is defined as the proportion of patients with a best overall response (BOR), defined as confirmed complete response (CR) or partial response (PR). BOR was defined as best response recorded from the start of treatment (C1D1) until progression or start of new anti-tumour therapy, whichever came first (source footnote, Table 9, Document B, CS). The company report that in the pooled cohort, lorlatinib led to ORR of 40.3% (95% CI 32.1, 48.9) with a majority achieving tumour shrinkage (full details are provided in Table 12, document B, CS). The company report that almost half (47.9% [95% CI 37.5%-58.4%]) of patients with brain metastases achieved a tumour response to lorlatinib with the majority experiencing tumour shrinkage (full details provided in Table 13, Document B, CS).

4.2.2 Secondary outcome: time to tumour response (TTR and IC-TRR)

Time to tumour response (TTR) was defined as time from C1D1 to first documentation of objective response (CR or PR). IC-TTR was defined in the same way but considered only the brain as the disease site. In the 56 (40.3%) patients that had tumour response the company report that the median TTR was 1.4 months (range 1.2-16.6), with about 75% responding within 4 months (source Table 14, Document B, CS). In those which had brain metastases, the median IC-TTR was 1.4 (range 1.2-16.2), source Table 15, Document B, CS.

4.2.3 Secondary outcome: duration of response (DOR and IC-DOR)

Duration of response (DOR) is defined as time from the first documentation of objective tumour response (CR or PR) to the first documentation of disease progression or death associated with any cause, whichever occurs first. The company report a summary of DOR in Table 16 and Figure 6 of Document B, CS. The median duration of response (95% CI) was 7.1 (5.6, 24.4) months. The ERG notes that the median DOR was longer in the EXP-4 cohort (median 12.5 months), compared with EXP-3B (5.6 months) and EXP-5 (7 months). The company report the same information for patients with brain metastases in Table 17, Figure 7, Document B, CS and show that in the pooled cohort, median IC-DOR was 14.5 months (95% CI, 11.1-not reached).

4.2.4 Secondary outcome: disease control rate (DCR and IC-DCR)

Disease control rate (DCR) has been defined by the company as the proportion of patients with disease control (CR, PR, stable disease) at 12 weeks and 24 weeks. IC-DCR is the proportion of patients with IC disease control (CR, PR, stable disease, considering only the brain as the disease site) at 12 weeks and 24 weeks. The company report the results for DCR and IC-DCR in Table 18 and Table 19 respectively of Document B, CS. In the pooled cohort, the DCR was 59.7% (95% CI 51.1-67.9) at 12 weeks and 43.2% (95% CI 34.8-51.8) at 24 weeks, with IC-DCR 73.4% (63.3-82.0) at 12 weeks and 55.3% (44.7-65.6) at 24 weeks.

4.2.5 Secondary outcome: progression free survival

Progression free survival is defined by the company as time from C1D1 to first documentation of objective disease progression or death on study due to any cause, whichever came first. The company submission, Document B, Figure 8 shows the Kaplan-Meier curve for progression free survival, and Table 20 reports that in the pooled cohort the median PFS is 6.9 months, 95% CI (5.4-8.2).

4.2.6 Secondary outcome: overall survival

Overall survival is defined as time from C1D1 to date of death due to any cause. In the pooled cohort, overall survival has median 20.4 months, 95% CI (16.1, NR). The probability of surviving to 12 months is 0.678 (95% CI 0.591-0.750) and 0.556 (0.155-0.306) to 18 months (source Table 20, Figure 9, Document B, CS).

4.2.7 Patient reported outcome: EORTC QLQ-C30/ EORTC QLQ-LC13

The company reported pooled analysis of the EORTC QLQ-C30 functioning scales for all the EXP cohorts, EXP-1:6, consisting of 255 patients, using data from the 15 March 2017 data cut. During the clarification process, the ERG expressed concern that an older data cut was used, compared to efficacy analysis (February 2018 data), and that all the cohorts were used, not just EXP-3B:5. In response (clarification question A4), the company provided updated tables for theses outcomes using the February 2018 data cut and provided the information for each of EXP-3B, EXP-4 and EXP-5 cohorts separately as well as pooled. Data presented for the later cut (Pfizer documents provided in response to clarification A4), showed similar results to the original CS and the ERG are satisfied that the data presented in the CS provide evidence that lorlatinib improves/keeps stable key patient-reported outcomes.

Using the March 2017 cut, the company reported the proportion of patients improving (≥10 points), remaining stable and worsening when compared to baseline for the global quality of life and the functional scales (Table 21, page 51, CS). The majority of patients had improved (42.4%) or remained stable (38.0%) for the global QoL score, with the majority also improving or remaining stable for each of the functioning scales (physical, role, emotional, cognitive, social). The company also report that the majority either improved or remained stable for each of the symptoms measured by QLQ-C30 and QLQ-LC13 (Table 22, Document B, CS). Key lung cancer symptoms reporting improvements were coughing (42.7%), pain in chest (29.8%) and dyspnoea (27.5%), as measured by QLQ-LC13.

4.2.8 Adverse reactions

Safety data were presented for all patients who received lorlatinib at 100 mg once daily in Study 1001, as of data cut 2 February 2018. The company state that this consists of 295 patients (17 from phase 1, 275 phase 2 and 3 from Japan lead-in cohort). In addition, the company present the safety data for the 139 patients in the EXP-3B:5 pooled cohort and it is these data which we focus on here. The median duration of lorlatinib was 16.3 months for the 100mg OD group, and 10.1 months for the pooled EXP-3B:5 cohort.

In the pooled EXP-3B:5 cohort, dose reductions and temporary discontinuations due to AEs occurred in [redacted] and [redacted] respectively. These were comparable to the 100mg OD group (Table 27, Document B, CS). Table 28, Document B, CS describes the specific AEs in both the 100mg OD group and for the EXP-3B:5 cohort. The proportions for each event type are comparable so in this ERG report, we present information on EXP-3B:5. The most common AEs were hypercholesterolemia ([redacted]), hypertriglyceridemia ([redacted]), oedema ([redacted]), peripheral neuropathy ([redacted]), with all other AEs reported in [redacted] or less of the EXP-3B:5 cohort. [redacted] of patients experienced a grade 5 AE, with [redacted] grade 3/4.

Serious adverse events occurred in [redacted] of the EXP-3B:5 cohort (full details Table 30, Document B, CS), the most common being disease progression [redacted]. Table 31, Document B, CS reported [redacted] SAEs were considered a treatment related serious adverse event, with 6 grade 3 and 4 grade 4 treatment related SAEs, none were fatal.

In the pooled EXP-3B:5 cohort, [redacted] of patients permanently discontinued lorlatinib treatment due to AEs (Table 32, Document B, CS) and this was a comparable percentage to the 100mg once daily group. Table 33, Document B, CS shows that [redacted] experienced dose reductions because of an AE, again comparable to the 100mg OD group.

The company conclude that *'safety data from Study 1001 demonstrate that lorlatinib was generally tolerable and when needed, AEs were manageable through dosing delay, dose reduction and/or standard supportive medical therapy'*. The ERG agrees with the company's conclusions.

4.2.9 Critique of evidence submitted for lorlatinib

The company present efficacy data for lorlatinib from a single phase two study of a single arm (Study 1001). No studies are presented which directly compare lorlatinib with any of the comparators specified in the NICE final scope. The company indicate that the only relevant comparator is chemotherapy. The ERG disagrees with this statement and consider ACBP a relevant comparator too. The ERG is of the opinion that the main limitation of the current assessment is that the evidence base for the

clinical effectiveness of lorlatinib relies solely on a small (n = 139) single arm study, which contains no UK based participants. The company present a MAIC to compare lorlatinib with chemotherapy (discussed in [redacted], Document B, CS); however, they do not use the MAIC results for their base case economic model.

The company present pooled data for cohorts EXP-3B, EXP-4 and EXP-5 (EXP-3B:5). The ERG agree that this best represents the current target population for lorlatinib and were happy with the decision to pool the cohorts. The ERG agree that EXP-1, EXP-2, EXP-3A were not relevant for this assessment as the prior treatment pathways do not match the target licensed population.

The ERG were initially concerned that the data cut used for efficacy date was February 2018 (nearly 18 months ago); however, at clarification the company confirmed that these are the most recent data available and that new data are not available until end of 2019, with final data ready in September 2020. The original CS presented data for quality of life outcomes based on an even earlier data cut (March 2017) but at clarification, the company provided Pfizer produced output on the more recent February 2018 data cut (see section 4.2.7 above).

4.3 Critique of trials identified and included in the indirect comparison and/ or multiple treatment comparison

4.3.1 Comparison with chemotherapy

The only relevant comparator considered by the company was chemotherapy, and no head to head trials were found. The evidence for the comparator of chemotherapy in ALK-positive NSCLC patients was presented for the ALUR, ASCEND5 and PROFILE 1001/1005 studies. Full details on these studies can be found in Appendix D, CS.

The ALUR trial compared alectinib (600mg twice daily) with chemotherapy (pemetrexed 500mg/m^2 or docetaxel 75mg/m^2 every 3 weeks), while ASCEND5 compared ceritinib (750mg per day) with chemotherapy (pemetrexed 500mg/m^2 or docetaxel 75mg/m^2 every 21 days). Participants in both studies had already had two lines of therapy (one line of platinum-based doublet therapy (PDC) and one of

crizotinib). The company pooled data from the chemotherapy arms of ALUR[2] and ASCEND5[3] for the PFS survival outcome within the MAIC as they reported that the baseline characteristics of the two trials were broadly similar. The ERG had concern over the use of these two studies as the evidence base for chemotherapy for the following reasons:

- all patients in ALUR/ASCEND have had PDC previously, which may not be relevant for the target population. ERG clinical opinion is use of crizotinib is falling and questioned whether these studies were the best source of comparator evidence.
- the ERG clinical expert has the opinion that while response rates on pemetrexed and docetaxel are likely to be similar, docetaxel has greater toxicity and the expert had uncertainty over their equivalence for pooling
- the ERG clinical expert did not agree with the assumption that PDC is equivalent to pemetrexed or docetaxel. The opinion is that PDC is superior to the single agents, and patients in the ALUR and ASCEND have already had the superior PDC treatment prior to study entry. The company offered a counter argument that patients in these trials were exposed to only one prior ALK TKI (crizotinib), whereas the population eligible for lorlatinib may have been exposed to two or more and so might be expected to have a worse efficacy outcome (as suggested by some clinical experts). However, the ERG remains concerned about the potential for underestimating the efficacy of PDC.

The company report that the ALUR and ASCEND5 did not provide any data for OS (page 54, Document B, CS). However, Appendix D and the publications for ALUR and ASCEND5 indicate that data for overall survival appeared to be available. It is not clear to the ERG why these data were not used by the company. Instead, the company undertook a retrospective analysis of the crizotinib arm of the PROFILE 1001 and PROFILE 1005 for the subgroup of patients receiving systemic therapy (likely chemotherapy) after progression on crizotonib. The ERG is concerned for the following reasons:

- the patient population previously treated with crizotinib were earlier dismissed by the company as being relevant to the licenced population. ERG clinical opinion is use of crizotinib is falling, and the current relevance of this population is questioned.

- the subgroup utilised here consists of only 37 patients, and the majority of patients are reported to have received PDC prior to study entry
- the subgroup here are considered ‘likely’ to be receiving chemotherapy but are not confirmed to be receiving chemotherapy. It is also not clear what chemotherapy they received and if they did so, given the majority were treated with PDC prior to study entry, it is likely to be one of the single agents (e.g. pemetrexed or docetaxel.

These data were then used by the company to undertake a matching-adjusted indirect comparison (MAIC) for lorlatinib versus chemotherapy for progression free survival (PFS) and overall survival (OS). A MAIC allows and indirect treatment comparison to be made when treatments are not connected by a common comparator (section 4.4).

4.3.2 Comparison to ABCP

The company did not consider atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP) a relevant comparator, but on request from NICE provided a short appendix to the main CS detailing the comparison. The reasons for dismissing ABCP as a relevant comparator were: patient fitness and the high proportion of brain metastases, low expected update given no precedent of use in ALK-positive patients, lack of powered clinical evidence and consultations with practicing expert oncologists who suggested ABCP use would be limited to EGFR patients. The ERG disagree with the company‘s position and consider ABCP a reasonable option, and it has been approved by NICE for the treatment of ALK patients.

The company present minimal efficacy data to inform the cost-effectiveness comparison of lorlatinib versus ABCP. The data for ABCP comes from a single trial (IMpower150)[29, 35, 36] which compared ABCP with bevacizumab, carboplatin and paciltaxel in patients with stage IV non-squamous NSCLC. The company note that this data is not comparable to EXP-3B:5 from Study 1001, as the IMpower150 participants are predominantly EGFR majority (n = 41) with only 11 having ALK-positive status. Further details on the ABCP comparison are found in section 5.2.4 of this report.

4.4 Critique of the indirect comparison and/ or multiple treatment comparison

4.4.1 Description/critique of the MAIC

As the evidence for lorlatinib is limited to a single arm study, the ERG agree it is not possible to undertake standard indirect comparison. NICE Technical Support Document 18[36] (TSD18) recommends that a Matching-adjusted-indirect-comparison (MAIC) can be used in this type of situation and it is an unanchored MAIC which has been implemented by the company to compare lorlatinib to chemotherapy. TSD18 provides six recommendations that all unanchored population adjustments must meet to be considered robust[36]. The ERG will present each of these in turn with an explanation as to whether they have been met by the company in their submission.

1. Unanchored population adjustment may only be considered in the absence of a connected network of randomised studies or where a single arm is involved.

The ERG agrees that recommendation one above has been met by the company as Study 1001 is a single arm study and is the only evidence available.

2. Evidence should be provided that absolute outcomes can be predicted with sufficient accuracy in relation to the relative treatment effects and present an estimate of the likely range of residual systemic error in the 'adjusted' unanchored comparison.

The company stated that clinical feedback suggested the most important prognostic variables/effect modifiers to be used in the matching were ECOG performance status (0-1 vs >1), brain metastases (yes vs no) and race (Asian vs Non-Asian). In addition, the company undertook a series of cox regression models to assess the importance of eight different variables in predicting outcome using the lorlatinib individual patient data (see section D.1.4.2.2, Appendix D, CS). The eight variables were: sex (male, female), age group (18-44, 45-64, ≥65), race (Asian, white, other), ECOG performance status (0,1,2), brain metastases (yes, no), adenocarcinoma (yes/no), weight (<66kg, ≥66kg), body mass index (BMI) (<18.5, 18.5-24.9, >24.9).

The company undertook this process on the combined data from cohorts EXP-2, EXP-3A, EXP-3B, EXP-4 and EXP-5 (EXP-2:5). Kaplan-Meier curves are available for each of these variables for each of the outcomes (OS and PFS) in Figure 2-Figure 9, section D.1.4.2.2 of Appendix D. The company provided hazard ratios for each covariate/outcome combination (Table 21 and Table 22, page 76, Appendix D). The ERG asked at clarification for 95% confidence intervals to be supplied for these estimates, which the company provided in response to clarification A8 (reproduced here as Table 5 and 6). This analysis showed that ECOG performance status and BMI were possible important predictors of outcome.

Table 5 HRs and p-values from univariate Cox proportional hazards model for each covariate for lorlatinib patients in cohorts EXP-2: EXP-5 (reproduced from company Table 2, clarification response A8 and Appendix D, table 21)

Model	OS			PFS (ICR)		
	HR	95% CI	p-value	HR	95% CI	p-value
Sex (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (White)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
ECOG PS (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (2)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
Brain metastases (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (>24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (18.5-24.9)	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; EXP = expansion; HR = hazard ratio; ICR = Independent Central Review; OS = overall survival; PFS = progression-free survival

Note: p-values <0.05 are shown in bold

[redacted]Gender was not highlighted in the above analysis, but the commented in their clarification response (A13) that gender was consider important in the literature.[37] Following this analysis and combining with clinical opinion, the company concluded that ECOG performance status (0-1 vs >1), brain metastases (yes vs no), race (Asian vs Non-Asian) and gender (male vs female) were the relevant variables for the matching process within the MAIC. The ERG agrees with this conclusion.

Table 6 HRs and p-values from multivariate Cox proportional hazards model for each covariate for lorlatinib patients in cohorts EXP-2: EXP-5 (reproduced from company Table 3, clarification response A8 and Appendix D, Table 22)

Coefficient	OS			PFS (ICR)		
	HR	95% CI	p-value	HR	95% CI	p-value
Sex (male)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Age (continuous)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (other)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race (White)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ECOG PS (2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brain metastases (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adenocarcinoma (yes)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (>24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BMI (18.5-24.9)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: BMI = body mass index; ECOG PS = Eastern Cooperative Oncology Group performance status; EXP = expansion; HR = hazard ratio; ICR = Independent Central Review; OS = overall survival; PFS = progression-free survival

Note: p-values <0.05 are shown in bold.

3. Population adjustment methods (both propensity score weighting and outcome regression) should adjust for all effect modifiers and prognostic variables, in order to reliably predict absolute outcomes.

As discussed under recommendation two, the company adjusted for four characteristics: race, gender, ECOG and brain metastases. While the ERG agree that these variables are relevant, they cannot be sure this list is exhaustive, and that residual bias has been avoided.

4. Indirect comparisons must be carried out on the usual linear predictor scale used for the evidence synthesis of that outcome

This has been implemented the company through presentation of hazard ratios from the Cox regression models. The ERG confirm recommendation four has been met.

5. The target population for the decision problem must be explicitly stated and the population adjustment must deliver treatment effect estimates for that target population.

The company present matching (population adjustment) to both EXP-2:3A and separately EXP-3B:5 (target population). The reason behind matching on the EXP-2:3A patient population is that they are more in line with the patients within the ALUR, ASCEND5 and PROFILE 1001/1005 studies as they received both chemotherapy and crizotinib previously. The company indicate that EXP-2:3A is their primary matching cohort, but because EXP-3B:5 is the target population, they also carried out an analysis for that as well. The ERG are happy with this approach and the justification and agree recommendation five has been met.

6. Strict reporting of the assessment of covariate distributions, evidence of effect modifier status, distribution of weights and measures of uncertainty

The company present summary statistics for the relevant covariates for each of the studies, but do not provide the full covariate distribution as per the recommendations (e.g., histograms/box plots). The distribution of weights were provided by the company and the ERG agree they were acceptable. Measures of uncertainty were provided in the form of bootstrapped confidence intervals for the hazard ratio estimates. Unadjusted and adjusted estimates were provided as per recommendations. Therefore, the ERG were happy that recommendation six was met sufficiently by the company.

4.4.2 Results of the MAIC: lorlatinib vs chemotherapy

Following the matching process described in Appendix D, CS, the company presented the results in section B.2.8.4 (PFS) and B.2.8.5 (OS). The ERG noted a mistake within the MAIC for progression free survival in regard to the proportion of subjects in the ALUR study with ECOG PS 1/2. This should have been 68.6% instead of the reported 14.3%. In the clarification response (A9) the company acknowledged the error and updated the results (originally presented Table 25, CS). These updated results are presented in Table 7. This error had no impact on the cost-effectiveness as the results of the MAIC were not used in the base-case. The MAIC showed that treatment with lorlatinib provided a clear reduction in hazard, i.e. longer time to progression when compared to those treated with chemotherapy.

Table 7 Unadjusted and adjusted HR for PFS following the MAIC (reproduced from Table 4, clarification response A9)

Weighted matching cohort (Study 1001)	Naïve		Adjusted	
	HR	95% CI	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; EXP = expansion; HR = hazard ratio; *bootstrapped 95% CI

Table 8 provides the results of the MAIC for the outcome of overall survival. The company noted that the definition of brain metastases differed between Study 1001 and PROFILE, so they carried out the MAIC with and without brain metastases as one of the matching variables and obtained similar results. The results showed that lorlatinib is associated with a decreased hazard of mortality when compared to chemotherapy.

Table 8 Unadjusted and adjusted HR for OS following the MAIC (reproduced from Table 26, CS)

Weighted matching cohort (Study 1001)	Naïve		Adjusted (including brain metastases)		Adjusted (not including brain metastases)	
	HR	95% CI	HR	95% CI*	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio *bootstrapped 95% CI

4.4.3 Summary of the MAIC

In summary, the ERG considers the MAIC an acceptable method to compare the clinical effectiveness of lorlatinib to chemotherapy. If one assumes the evidence base is acceptable then the MAIC has shown clinical benefit of lorlatinib compared with chemotherapy for both PFS and OS. However, the ERG have concern over the evidence base used for chemotherapy (section 4.3.1), and therefore concern over the validity in the interpretation of the result.

The MAIC results are not used to inform the base case economic model.

4.5 Additional work on clinical effectiveness undertaken by the ERG

None.

4.6 Conclusions of the clinical effectiveness section

The company have provided evidence that lorlatinib is effective in prolonging time to progression and prolonging overall survival in patients with ALK-positive advanced NSCLC following progression from one or more previous ALK TKIs. The company provided sufficient evidence of a tolerable safety profile and evidence that lorlatinib provide stability or improvement in a number of important quality of life domains as measured by QLQ-C30 and QLQ-LC13.

The evidence for lorlatinib is limited to a single arm study, and thus a MAIC was undertaken (as recommended by NICE in these situations) and the ERG are happy the MAIC has been implemented correctly. However, as discussed above the ERG have

some have reservations over the evidence-base used for the comparator of chemotherapy.

In summary, the ERG agree with the company's conclusion on the effectiveness of lorlatinib versus chemotherapy subject to the following concerns:

- One small single arm study is the sole source of evidence for lorlatinib
- Chemotherapy is assumed by the company to be the only relevant comparator for the target population, but the ERG believe ABCP should have been considered a relevant comparator.
- ERG clinical opinion believes PDC is superior to pemetrexed and docetaxel monotherapy, but the company have made an assumption the different chemotherapy options have equal clinical benefit
- The use of PROFILE 1001/1005 to provide data for OS given the participants are 'assumed' to be on chemotherapy and not known to be. The type of chemotherapy is unknown. Overall survival data were available within ALUR/ASCEND but were not used by the company.
- the company do not use the MAIC results in the base case analysis of the economic model.

5 Cost effectiveness

5.1 ERG comment on company's review of cost-effectiveness evidence

5.1.1 State objectives of cost effectiveness review. Provide description of company's search strategy and comment on whether the search strategy was appropriate. If the company did not perform a systematic review, was this appropriate?

One objective of the review was to identify previous studies of the cost-effectiveness of lorlatinib in the licensed indication. The search strategy was described in Appendix G.

The search strategy seems appropriate. While the search was conducted in August 2018 and not updated, the ERG agrees no relevant studies of cost-effectiveness of lorlatinib have been published.

The systematic review also searched for information on previous modelling, utility values and on resource use and costs; these are considered under the relevant headings of this report and only the search for previously published economic evaluations was considered here.

5.1.2 State the inclusion/ exclusion criteria used in the study selection and comment on whether they were appropriate

The criteria are set out in Appendix G (Table 44, commencing on page 103 of the company appendices). These seemed appropriate.

5.1.3 What studies were included in the cost effectiveness review and what were excluded? Where appropriate, provide a table of identified studies. Please identify the <u>most important</u> cost effectiveness studies

The review identified 20 economic evaluations of medicines for ALK-positive NSCLC. None were of lorlatinib.

5.1.4 What does the review conclude from the data available? Does the ERG agree with the conclusions of the cost effectiveness review? If not, provide details

The review concluded that no published studies of lorlatinib were identified up to August 2018. The company judged that updating the review would not identify any new publications and the ERG accepts this view as far as journal articles are concerned. However:

1. The review appears to have missed TA 406[23] (crizotinib in previously untreated disease); the excluded studies are in Appendix H.1.1.3 on page 113 but does not seem to be mentioned. (TA 422[26] was a CDF review of TA 296[38], which was also not identified.)
2. It is feasible that a conference abstract could have been reported in the 12 months since the review was undertaken and ideally the company would have undertaken a search of this specific source e.g. ISPOR meetings in that period.
3. The ERG agrees there do not appear to be any reports from other HTA agencies such as ICER on lorlatinib.
4. The company review appropriately identified previous NICE TAs 395[27] and 422[26] (ceritinib after crizotinib and crizotinib after one previous treatment respectively) within ALK-positive NSCLC, but because the review was not updated it did not identify TAs 500[24] (ceritinib in previously untreated), 536[25] (alectinib in previously untreated) or 571[21] (brigatinib after one previous treatment).

5.2 Summary and critique of company's submitted economic evaluation by the ERG Suggested research priorities

5.2.1 NICE reference case checklist (Table only)

Table 9 NICE reference case

Attribute	Reference case and TA Methods guidance	Does the *de novo* economic evaluation match the reference case
Comparator(s)	Refer to NICE scope for suggested comparators in: 1) people who have not had previous chemotherapy; 2) people who have had previous chemotherapy (but not a PD-L1 immunotherapy); and 3) people who have had previous treatment with an immunotherapy (PD-L1 inhibitor)	The company has included the comparators that were listed in the scope for those who have not had previous chemotherapy or previous treatment with an immunotherapy. The company argue that first line use of chemotherapy in the ALK+ NSCLC population is rapidly diminishing, and most patients eligible for lorlatinib will not have had prior chemotherapy or immunotherapies but will have progressed primarily on alectinib as the first line treatment. The ERGs clinical expert broadly agrees with this assertion.
Patient group	People with advanced ALK-positive NSCLC that has: progressed after treatment with alectinib or ceritinib as the first ALK-tyrosine inhibitor; Or progressed after treatment with crizotinib and at least one other ALK-tyrosine kinase inhibitor.	The company submission covers the relevant patient population.

Perspective costs	NHS and Personal Social Services	Yes
Perspective benefits	All health effects on individuals	Yes. Carers not included
Form of economic evaluation	Cost-effectiveness analysis	Yes, a cost-utility analysis is performed.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes, a life time perspective is taken.
Synthesis of evidence on outcomes	Systematic review	Yes, systematic reviews were carried out to inform key parameters. Uncertainties arise from the single arm design of Study 1001 and the limited availability of data to inform the comparative effectiveness of PDC and ABCP in the relevant population.
Outcome measure	QALYs	Yes
Health states for QALY	Described using a standardised and validated instrument	The health status in the model states (progression free and progressed) is based primarily on EQ-5D response data from NSCLC patients. However, the utility value applied for the pre-progression state on lorlatinib is derived by mapping from the EORTC QLQ-C30 questionnaire.
Benefit valuation	Time-trade off or standard gamble	Yes, the UK EQ-5D TTO tariff is applied.
Source of preference data for valuation of	Representative sample of the public	Yes, UK general population.

changes in HRQL		
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes
Probabilistic modelling	Probabilistic modelling	Yes, but results only presented for the company's base case comparison against PDC.
Sensitivity analysis		Covered the main sources of uncertainty, but it is the ERG's opinion that not all uncertainties were adequately addressed through sensitivity analysis.

5.2.2 Model structure

The company submission used a partitioned survival model to estimate costs and benefits. The health states were progression-free survival, post-progression survival (PPS) and dead.

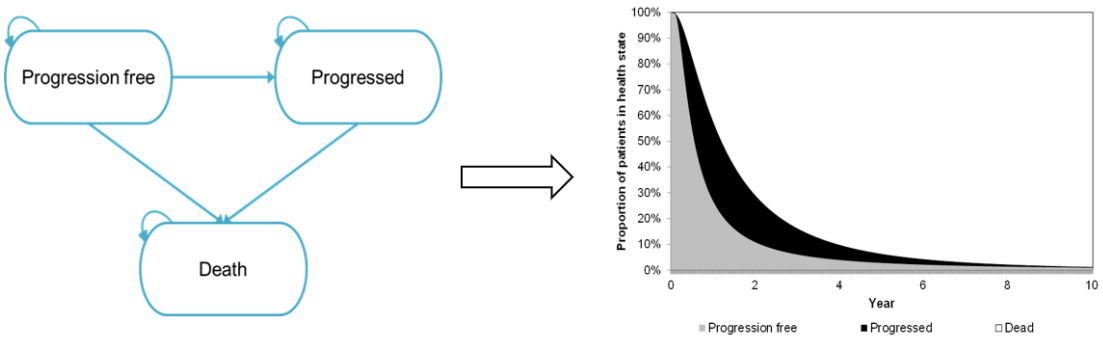


Figure 2 Company model structure (Reproduced Figure 19, Company submission, Document B, page 84)

The structure and states reflect the economic models previously used in all the NICE STAs of medicines for ALK-positive NSCLC (TAs 395[27], 406[23], 422[26], 500[24], 536[25], 571[21]). The only exception is that TA 536 divided progression into 'CNS progression' (typically metastatic disease in the brain) and non-CNS progression. This could be potentially relevant for lorlatinib if type of progression is proportionally different among those who progress on lorlatinib and PDC or ABCP.

5.2.3 Population

The patient population in the company's economic model is taken from the following table (Table 10), which describes all patients in Study 1001. The company make the case that the cohorts in the study that match the license are 3b, 4 and 5.

Table 10 Populations in Study 1001 (Source: Table 36, Company Submission, Document B, page 83)

ALK/ROS1 status	Cohort	Used in model	Prior treatment regimen
ALK-positive	EXP-1	No	Treatment-naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ALK TKI therapy)
	EXP-2	No	Patients relapsing after crizotinib therapy only
	EXP-3A	No	Patients relapsing after crizotinib therapy and one or two prior regimens of chemotherapy
	EXP-3B	Yes	Patients relapsing after one ALK TKI therapy other than crizotinib with or without any number of prior chemotherapy regimens
	EXP-4	Yes	Patients relapsing after two prior ALK TKI therapies with or without any number of prior chemotherapy regimens
	EXP-5	Yes	Patients relapsing after three or more prior ALK TKI therapies with or without any number of prior chemotherapy regimens
ROS1-positive	EXP-6	No	Treatment naïve patients (no prior chemotherapy in the metastatic disease setting, and no prior ROS1 inhibitor therapy) or patients who had any number of prior cancer therapies (chemotherapy and/or ROS1 inhibitor therapies)

Abbreviations: ALK = anaplastic lymphoma kinase; EXP = expansion; ROS1 = ROS proto-oncogene 1; TKI = tyrosine kinase inhibitor

Source: Company Submission, Document B, Table 36, page 83.

The population described in the Final Scope is "People with advanced ALK-positive NSCLC that have:

- progressed after treatment with alectinib or ceritinib as the first ALK-tyrosine inhibitor,

  or

- progressed after treatment with crizotinib and at least one other ALK- tyrosine kinase inhibitor."

EXP-6 is clearly not relevant because it is for NSCLC that is ROS-1 positive. EXP-1 is for treatment naïve ALK-positive patients and hence is also not relevant. EXP-2 is for relapse after crizotinib only, and the license requires the patients fail after crizotinib and at least one other TKI. EXP-3A patients failed after crizotinib and chemotherapy, not another TKI, so is also outside of the license.

The ERG therefore agrees that cohorts EXP-1, -2, -3a and -6 from Study 1001 are all outside of the final scope.

The company submission then combines all three cohorts (3B, 4, 5) into one group for the purpose of producing an estimate of effectiveness.

5.2.4 Interventions and comparators

The intervention in the company submission was lorlatinib 100mg once daily. Duration on treatment was informed by modelling of PFS and time on treatment data from Study 1001. From the EPAR SmPC[39], the recommended duration of treatment is as follows:

"Treatment with lorlatinib is recommended as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity."

The options for comparator were specified in the final scope by whether patients have been previously treated with chemotherapy and/or a PD-L1 immunotherapy.

For those who have not had previous chemotherapy, the final scope specified:

- Pemetrexed with cisplatin/carboplatin (adenocarcinoma or large cell carcinoma only), with or without pemetrexed maintenance
- Atezolizumab with bevacizumab, paclitaxel and carboplatin (non-squamous only) [subject to NICE appraisal]

For people who have received previous chemotherapy (but not a PD-L1 immunotherapy), the final scope specified atezolizumab, pembrolizumab and 'best supportive care' (BSC) as comparators.

For people who have had previous treatment with an immunotherapy (PD-L1 inhibitor), nintedanib with docetaxel (adenocarcinoma only), docetaxel and best supportive care were listed as comparators in the final scope.

The company submission reports clinical expert views as being that for ALK+ NSCLC, targeted ALK TKIs are preferred ahead of other therapies, with the aim being to maximise the time patients are treated with these. Where available ALK TKIs are exhausted, the company note that clinicians generally favour PDC ahead of immunotherapy (with or without chemotherapy). They also note that clinical expert opinion consistently suggests that the pathway beginning with the second generation ALK-INH alectinib is quickly becoming standard care, and that the pathway beginning with chemotherapy is therefore becoming less common, representing "a small and rapidly shrinking pool of patients". The company also note that the use of the immuno-oncology medicine, atezolizumab, is likely to be low because of the limited evidence in ALK-positive disease, and 66.9% of patients in Study 1001 have brain metastases at baseline and hence are not suitable.

The company therefore conclude that chemotherapy, which they identify as pemetrexed plus carboplatin or cisplatin (PDC), is the most relevant comparator for lorlatinib in their submission. The company also submitted an addendum to their main submission which provided a comparison with the atezolizumab combination regimen (atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP)).

The ERG's clinical advice is that:

- *alectinib is probably the most widely used medicine in previously untreated patients*
- *the pathway where chemotherapy is used first is less likely as ALK testing is now routine*
- *for the diminishing population who have crizotinib as their first ALK TKI, the next line of treatment would probably be brigatinib (it may be more effective than ceritinib and has a better side-effect profile)*
- *lorlatinib will be given after other ALK-targeted treatments*

- *the atezolizumab combination regime (ABCP) is a feasible comparator for lorlatinib*
- *chemotherapy is an option in later lines but where there is a choice its use is delayed as long as possible because of side-effects*

The ERG's conclusions are that the comparison with PDC is appropriate, that other TKIs are not comparators, and that a comparison with ABCP is relevant and should be considered as part of the base-case and not as a secondary analysis.

In costing the PDC regime, the company submission specifies that this is to be followed by pemetrexed maintenance therapy for those remaining progression free after 6 cycles. The ERG note this is generally in line with recommendations from NICE TA402 (Pemetrexed maintenance treatment for non-squamous non-small-cell lung cancer after pemetrexed and cisplatin)[40] and NICE TA190 (Pemetrexed for the maintenance treatment of non-small-cell lung cancer)[41]. However, NICE TA402 states that ECOG performance status should be 0 or 1 at the start of maintenance treatment[40]. Therefore, the assumption that all patients move on to maintenance pemetrexed if they remain progression free after six treatment cycles of PDC may be questionable.

The ERG also notes that nivolumab and nintedanib with docetaxel are mentioned in NICE NG122[42] as treatment options following first-line chemotherapy. Clinicians do not seem to regard these as standard treatments at this stage in the pathway and they have not been considered further in the model. Rather, atezolizumab and pembrolizumab are considered as subsequent treatments to PDC in the company model.

5.2.5 Perspective, time horizon and discounting

The perspective in the economic evaluation provided by the company was the NHS plus personal social services.

The ERG agrees this matches the NICE Reference Case.

The time horizon in the base case of the economic evaluation was 20 years. Patients in the relevant cohorts of Study 1001 were aged 52.5 on average when treatment started (from Table 11 on page 41 of Document B) so any surviving patients would be age 72.5 (52.5 plus 20) at termination of the model. However, less than 1% of the cohort are surviving in both arms of the model by this time point. Therefore, the ERG accepts the 20-year time horizon is acceptable for the base case.

The discount rate used in the company submission was 3.5% per annum (Section B.3.2.3 in Document B, page 83). This is consistent the NICE Reference Case.

5.2.6 Treatment effectiveness and ***extrapolation***

Study 1001 was non-comparative and recruited different cohorts of patients, the relevant ones for the licensed indication being distinguished by previous treatments received. It is the only source of efficacy data for lorlatinib and hence was used as the basis for estimates of effectiveness over an extended time horizon and compared to a relevant alternative.

PFS: lorlatinib

Data from the clinical study were presented in the submission in Document B, Figure 22 and Table 40 on page 94.

Standard parametric curve fits were undertaken by the company and clinical experts from the UK were asked which curve they felt was most appropriate: the company reported they favoured generalised gamma or Gompertz curves. In the base-case the generalised gamma was selected on the basis of visual and statistical fit to the observed data plus long-term plausibility (seemingly meaning the endorsement of the clinicians consulted). The generalised gamma was described as in the middle of the range of estimates for all curves (page 93, Document B).

OS: lorlatinib

OS data from the clinical study were presented in Figure 39 and Table 44 of the CS (document B, p111). The clinical data were extrapolated by fitting parametric curves. An assessment of the fit of the curves was conducted in line with NICE TSD 14[43] guidance. Following this, the opinions from two clinical experts were sought (a

description of the clinical validation process, along with issues with the process which have been identified by the ERG, is contained within Section 5.10). Upon request for clarification by the ERG, the company updated Table 44 to include the proportion alive at 10 years. This table is reproduced as Table 11 below.

Table 11 Updated Table 44: Mean, median and landmark values and AIC and BIC statistics for lorlatinib OS parametric survival models

Model	AIC	BIC	Mean OS (months)	Median OS (months)	Proportion alive at each landmark value (%)					
					6 months	1 year	2 years	3 years	5 years	10 years
Generalised gamma	[redacted]									
Exponential	[redacted]									
Weibull	[redacted]									
Log-normal	[redacted]									
Log-logistic	[redacted]									
Gompertz	[redacted]									

Abbreviations: AIC = Akaike information criterion; BIC = Bayesian information criterion; OS = overall survival

From Table11, it can be seen that the exponential curve has the best statistical fit to the observed clinical data using both the AIC and BIC, although by a small margin. The company argue that selecting a parametric survival curve based primarily on information criterion is not appropriate in this case due to the limited range of information criterion values observed across the six curves. Additionally, the company argue that the information criterion values do not appear to be strongly related to landmark values of the extrapolated curves.

Rather than select a parametric OS curve based solely on information criterions, the company sought the opinions of two clinical experts. One of the clinical experts stated an expectation that 10-year OS for lorlatinib would be around [redacted], and that the [redacted] prediction of the exponential curve was overly pessimistic.

[redacted]. However, the company adopted the generalised gamma curve for extrapolating data in the base case.

The ERG recognises the difficulty of extrapolating limited clinical data substantially beyond the observed period. Although the company found a consensus amongst the two clinical experts they consulted, the ERG's clinical adviser believed that the [redacted] *projected survival at 10 years for lorlatinib was optimistic given the previous treatment history and believed* [redacted] *to be more plausible. The ERG supports the company's decision not to adopt the most optimistic extrapolation for lorlatinib OS, despite consensus amongst the clinical experts they consulted. Based on both the ERG's clinical advice and the measures of statistical fit (AIC and BIC), the ERGs opinion is that the extrapolation based upon the exponential distribution cannot be disregarded. However, given the paucity of clinical data and substantial doubt regarding the most appropriate extrapolation, the company has adequately addressed this within their scenario analysis.*

Comparative clinical effectiveness

The company made decisions about:

- Which clinical study data to use to represent the comparator arm
- Which method to use to compare lorlatinib with the 'usual care' data
- How to fit parametric curves to the data for lorlatinib and the comparator arm

Selection of clinical study data for comparator arm

The company submission included a systematic review to identify potentially relevant clinical studies. There were no studies where PDC was used in pre-treated ALK+ disease. The company's approach was to only consider studies of patients with pre-treated ALK+ disease, and the only chemotherapy treatments explicitly identified in available studies were pemetrexed monotherapy and docetaxel monotherapy. The company submission assumed that the data for these treatments would apply to PDC as well.

The selected studies were ALUR and ASCEND-5 for PFS and a retrospective analysis of PROFILE 1001/1005 for OS:

- ALUR and ASCEND-5 were RCTs in pre-treated ALK+ NSCLC patients of alectinib (ALUR) and ceritinib (ASCEND-5), both versus investigator's choice of either iv pemetrexed 500 mg/m2 or docetaxel 75 mg/m2, both every

3 weeks. Both studies were open-label, both allowed crossover and both had PFS as the primary endpoint.

- PROFILE 1001 and PROFILE 1005 were single-arm studies of crizotinib treatment, totalling 414 patients (figures from Ou 2014). The analysis was of 194 patients whose disease had progressed and was originally intended to compare patients treated with crizotinib after progression with patients who stopped crizotinib (n=120 versus n=74). The company submission argues it is the latter group who best represent the comparator arm for the lorlatinib economic evaluation because the patients have had a TKI and then get a non-TKI treatment.

ERG commentary

The ERG makes the following points about the company's choice of data of efficacy data for the comparator:

1. The ERG agree there are no studies of PDC in ALK+ patients pre-treated with ALK TKI.

2. The ERG also agree that the PFS data for pemetrexed monotherapy and docetaxel monotherapy in pre-treated patients are relevant when judging the most plausible level of effectiveness for PDC in pre-treated patients.

3. However, the ERG's clinical expert advice is that PDC would be more effective than either of the monotherapy regimes.

4. The ERG is aware of another RCT in NSCLC comparing PDC to pemetrexed monotherapy which confirmed PDC was more effective (Smit et al, JCO 2009 27 2038). There may be others, the search was not comprehensive.

5. Of the pooled sample from ALUR and ASCEND-5 (n=151), 77% were from ASCEND-5. Across the two studies, 147 patients received treatment with 98 choosing docetaxel (67%) and 49 pemetrexed. This is of concern because the published report on the ASCEND-5 RCT comments, "In previous studies, patients with ALK-rearranged non-small-cell lung cancer have been shown to be particularly responsive

to pemetrexed[44, 45]. Thus, the higher proportion of patients given docetaxel (63%) in this study than in the PROFILE 1007 study (41%) might have led to a worse overall outcome in the chemotherapy group from this study than in the PROFILE 1007 study."[3]. The preponderance of patients treated with docetaxel in the pooled sample suggests using these data to estimate the effectiveness of PDC in this population will result in an under-estimate of PFS.

6. The use of the retrospective analysis of PROFILE 1001 and 1005 to inform OS for PDC has several weaknesses:

- *The number of patients who stopped crizotinib on progression and received a subsequent systemic therapy is only 37[46] and the small sample size means there is considerable uncertainty in the interpretation of the results.*
- *The Ou paper reports these 37 patients received systemic therapy but it does not say what this was. 96% of patients were reported to have received previous platinum therapy prior to entry into the study[46] (Table 1) – assuming this to be PDC it seems unlikely PDC would be used again therefore the data are not directly relevant. As Pfizer sponsored the PROFILE studies and Ou's work it was not clear why the type of therapy received by the 37 patients was not reported.*
- *Of the 194 who progressed on crizotinib, the group who continued crizotinib after progression could be those who were the best responders to a TKI and hence the sample is skewed.*
- *Crizotinib is a 1st generation TKI and its use in England and Wales is falling. Patients potentially considered for lorlatinib are likely to have been pre-treated with a 2nd generation TKI instead which raises questions about the generalisability of the findings to modern NHS practice.*

Taken together this suggests the results could under-estimate what PDC would achieve in this setting.

7. The company submission took PFS data from one pair of studies and OS data from another pair of studies. Ou reports time to progression as well as OS; ALUR and ASCEND-5 report OS as well as PFS.

In terms of progression, Ou reports a median time of 5.7 months[46], but this is an average of patients receiving systemic therapy and BSC; only considering the former group would seem likely to have raised this figure. This is considerably above the median PFS in ALUR and ASCEND-5 which was around 1.5 months. If Ou is relevant for the OS part of the analysis, it is not clear why the data are not also relevant for the PFS analysis.

In terms of OS, the data from ALUR and ASCEND-5 were ignored, which could be argued to be because of the high rate of crossover, but an effort could have been made to adjust for this. In ASCENED-5 there were more deaths at the interim analysis on ceritinib than on chemotherapy.

8. PDC has been included in RCTs in ALK+ NSCLC but only in previously untreated patients; however, the results could still be relevant if there was evidence that the relative treatment effect between a TKI and PDC did not vary depending on treatment history. Based on a meta-analysis in 2018[47], PDC has been used in RCTs of previously untreated ALK+ patients in the following studies:

- *ASCEND-4[35] – RCT against ceritinib, HR for PFS 0.55, 95% CI 0.42 to 0.73*
- *PROFILE 1014[48] – RCT against crizotinib, HR for PFS 0.45, 95% CI 0.35 to 0.60*
- *PROFILE 1029[49, 50] – RCT against crizotinib, HR for PFS 0.42, 95% CI 0.286 to 0.565*

Of these, ASCEND-4 is more relevant because ceritinib is a 2nd generation TKI, as opposed to crizotinib which was used in the other RCTs. All of these studies would have been identified in the company's systematic review but then excluded for being in previously untreated patients. The ERG agrees that this is an issue but the hazard ratios compared to TKIs are still potentially relevant to help form a view of the plausible range for the comparative clinical effectiveness of lorlatinib, under the assumption the relative treatment effect is approximately equal irrespective of previous treatment history.

Method to compare lorlatinib to PDC

Three methods were considered to estimate PFS and OS over time with pemetrexed-plus carboplatin or cisplatin. These were:

1. Hazard ratios estimated using a matching adjusted indirect comparison (MAIC)
2. Hazard ratios estimated using an unadjusted indirect comparison (UIC)
3. Direct estimation of PFS and OS over time by fitting independent parametric models (IPMs) directly to clinical study results.

In each case, ALUR and ASCEND-5 were used for PFS, and PROFILE 1001 and 1005 for OS.

The company recognised that there was a potential issue because the studies used to provide data for PDC were better aligned to the treatment history of cohorts 2:3A in Study 1001 than to cohorts 3B:5. Therefore each of the three methods was used to provide estimates to the two lorlatinib cohorts, as described in Figure 21 from the company's submission (page 92 of Document B); reproduced as Figure 3 below.

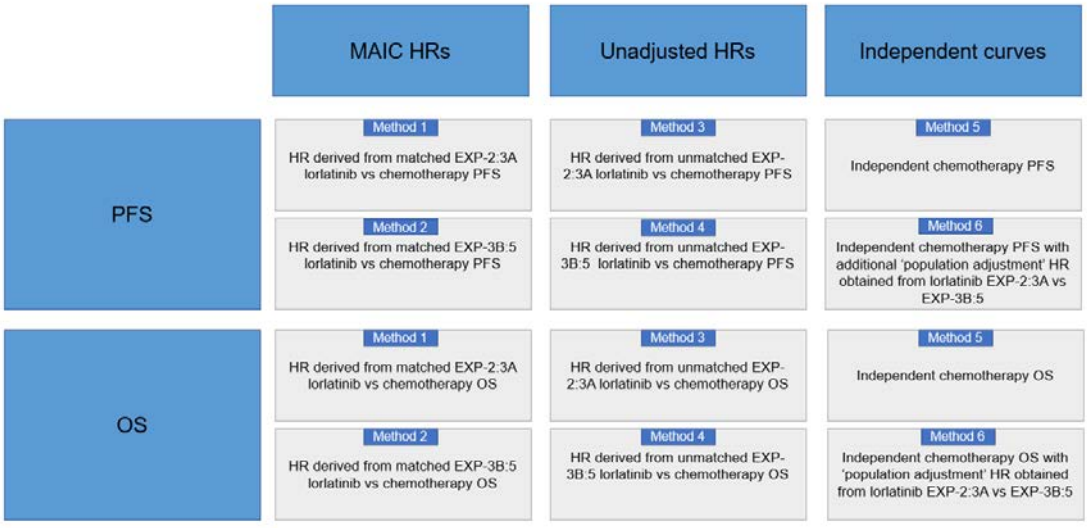


Figure 3 Summary of methods explored to derive comparator evidence (Source, Figure 21, company submission, document B, page 92)

For PFS the results of the unadjusted indirect comparison and of the MAIC were as shown in Table 12 below.

Table 12 Unadjusted and adjusted HR results for overall survival (Source: Table 25, company submission, Document B, page 62)

Weighted matching cohort (Study 1001)	Naïve		Adjusted (including brain metastases variable)		Adjusted (not including brain metastases variable)	
	HR	95% CI	HR	95% CI*	HR	95% CI*
EXP-2:3A	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EXP-3B:5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations: CI = confidence interval; HR = hazard ratio

*bootstrapped 95% CI

Rather than utilising the hazard ratios derived from the unadjusted comparison or MAIC, the company opted to use Method 5 (Figure 3) in their base case, using the following logic:

- The chosen methods for PFS and OS should be consistent – for example, it would be inconsistent to prefer an unadjusted comparison to 2:3A for PFS and an adjusted comparison to 3B:5 for OS.
- Proportional hazards may not hold for Methods 1 to 4
- Based on clinical opinion, PDC performance would be comparable in patients pre-treated with crizotinib vs pre-treated with a 2nd generation inhibitor.
- However, as methods 2 and 4 may have an issue with proportional hazards then method 5 is preferred.

Method 5 relied on fitting independent parametric curves to the PFS data from ALUR and ASCEND-5, and the OS data from PROFILE 1001 and 1005 for OS. The relevant published KM curves were digitised and the IPD were reconstructed, allowing alternative parametric distributions to be fitted. For PFS a log-logistic curve was selected based on having the best visual and statistical fit to the observed data (see Table 42 of the CS, document B). The ERG is satisfied that it offers the best

statistical fit based on the AIC and BIC. The same overall approach was followed for OS, and the log-normal distribution was selected based on statistical and visual fit (see Table 46 of the CS, document B). Again, the ERG is generally satisfied with the curve selection process, if not the suitability of the data upon which the fitting was based.

Whilst the final method (method 6) also utilised these independently fitted comparator curves, it included adjustments to account for the fact that the comparator sources reflected populations with fewer prior treatments than the EXP-3B:5 cohort. These adjustments were made my applying hazard ratios reflecting the difference in PFS and OS between the EXP-2:3A and EXP-3B:5 cohorts from Study 1001. However, as noted above, the company ultimately rejected this approach based on clinical advice suggesting that "*patients receiving PDC would be expected to perform equally poorly following treatment with crizotinib or a second-generation ALK TKI*" (P122 of CS). Thus method 5 was selected over method 6.

ERG commentary
The ERG welcomes the presentation of several methods and a number of different results as an aid to decision-making.

The ERG acknowledges the company's logic in its choice of a method; however, other logic could be applied e.g. an adjusted comparison is preferred to an unadjusted comparison and comparing to patients in cohorts 2:3A of Study 1001 is irrelevant because it is not the population covered by the license. This points to Method 2, the MAIC with comparison to cohorts 3B:5 as being the most relevant.

The methods for the two types of indirect comparisons (MAIC and UIC) were presented in Section B.2.8 of the company submission and are discussed in chapter 4 of this ERG report.

Whilst not explicitly discussed in CS, all the company's approaches for estimating comparative effectiveness give rise to a reduced hazard of death with lorlatinib in each cycle that persists throughout the model time horizon. The scenarios that relied on application of unadjusted or adjusted hazard ratios assumed proportional hazards

over entire time horizon. The company base case approach (method 5) results in a diminishing relative treatment effect over time in the model, but the hazard of mortality remains lower in the lorlatinib arm across the entire time horizon. Given the uncertainty associated with such extrapolations, the ERG explored the impact of applying more dramatic waning of the relative treatment effect, by setting the hazard of mortality in the lorlatinib arm equal to that in the PDC (or ABCP arm) from three years and five years.

5.2.7 Health related quality of life

Data collected in Study 1001

In Study 1001 the questionnaires EORTC QLQ-C30 and EORTC QLQ-LC13 were scheduled to be completed during each 21-day cycle of treatment. The completion rate for all questionnaires was [redacted] and all patients completed at least one questionnaire.

Mapping to derive the lorlatinib PFS utility value

Because the company decided not to include EQ-5D in the clinical study protocol, it was necessary to map the data that were collected to EQ-5D. A choice of algorithms was available, the company identifying five examples through a database of mapping functions collected in 2016. The five options were narrowed down to two using the following principles:

- The algorithm should map to the UK EQ-5D tariff
- The algorithm should have been derived from a sample containing some lung cancer patients
- The algorithm should be sufficiently clearly described that it can easily be applied to the current data set

The selected algorithm was that described by Longworth et al[51], which maps to EQ-5D-3L using UK tariff values, and gave an estimated utility value for PFS while on lorlatinib of [redacted].

ERG commentary

Mapping is always a second-best option compared to direct elicitation of EQ-5D in the clinical study. It introduces additional uncertainty in terms of algorithm selection, appropriateness, predictive power, etc.

The use of the 2016 mapping database to identify algorithms was a good starting point but, as a matter of good practice, the literature search should have been updated to capture any more recent studies.

Longworth et al was an NIHR-funded project to review generic and disease-specific tools for NICE decision-making and as such seems a plausible choice for the base case. However, the criteria should have included validation studies of the mapping functions (see e.g. Woodcock et al[52]). This article suggests that Longworth et al performs reasonably well, but points to possible issues with mapping worse health states.

Comparator arm (PDC): PFS

In the submission, the company could have applied the utility value for PFS from lorlatinib to time on PDC and progression-free; however, the company submission estimated a separate value instead, for two reasons:

- This is consistent with the findings of PROFILE 1007 [53]in previously treated ALK positive patients randomised to either crizotinib or chemotherapy (either docetaxel or pemetrexed monotherapy)
- The company note that within the HRQoL systematic literature review, seven out ten studies identified progression free treatment specific utilities, and four made a comparison between ALK TKIs and chemotherapy, with the difference ranging from 0.02 to 0.08).
- Lorlatinib is oral whereas chemotherapy is by iv infusion and the company assume a disutility to attending hospital.

The PFS value for PDC was based on PROFILE 1014[48] and was 0.72. The choice of PROFILE 1014 was justified because the comparator arm was PDC, it recruited ALK+ NSCLC patients, and the sample size was 171.

In sensitivity analyses values used included Zhou et al[54], TA395[27] and Blackhall et al[53] for PFS.

ERG commentary

The justification of a separate PFS value while on PDC is questionable given a lack of direct comparative evidence in the relevant population at the appropriate treatment line (following progression on second generation ALK TKI). The evidence from PROFILE 1007[53] is suggestive but there are differences, for example, chemotherapy being pemetrexed or docetaxel monotherapy rather than PDC. Also, patients in PROFILE 1007 were pre-treated with platinum-based chemotherapy and not an ALK TKI, and a relatively higher proportion were Asian in the pemetrexed group.

The second argument, that patients have higher utility on oral treatment compared to iv, should have been empirically tested.

Given the uncertainty with respect to the magnitude of any difference in utility between lorlatinib and PDC treated patients who have previously progressed on a second generation ALK TKI, and a lack of directly elicited EQ-5D data for lorlatinib at this stage, the ERG have performed further exploratory analyses whereby lorlatinib utility increments of 0.02 to 0.08 (the range reported by the company) are applied to the pre-progression PDC utility value (0.72) applied in the model.

The ERG notes the advantages stated for PROFILE 1014 as a source of utility value for PDC, but also believe the value reported by Blackhall from Study 1007 provides a plausible alternative.

PPS after progression on either treatment

The utility value for PPS was taken from the study by Labbe[55] and was 0.65. The main criterion for selecting a value was the number of ALK+ patients in the sample, or more precisely the number of confirmed ALK+ patients, because in some studies this was not separately specified. Labbe et al had 38 of 475 patients in the total sample who were ALK+.

In sensitivity analyses values used included those from TA422[26], LUME LUNG-1[56], and Zhou et al[54].

ERG commentary

The company's approach to selecting a study as a source for utility values in PPS assumes that having the ALK mutation is the most important factor, then selects the study with the most identified ALK+ patients. The ERG finds it equally plausible that for people with advanced NSCLC who have progressed after two or three lines of treatment, quality of life could be equally diminished, irrespective of genetic mutation status. Furthermore, the exact timing of the utility value applied from Labbe et al is unclear. It may reflect the health state utility of patients around the time of progression whilst still on treatment, making it less suited to representing utility across the whole time period in the progressed disease state.

From this standpoint, other sources of utility specific to the place in the treatment pathway become relevant. The study of Chouaid et al[57], cited above, reported progressive disease values of 0.59 and 0.46 specific to 2nd line and 3rd/4th line treatments of advanced NSCLC respectively. These values could both be applicable to patients in the progressed state of the company's model. In Nafees[58] 100 members of the UK public were interviewed to rate states in NSCLC using the standard gamble method; the mean value for progressed disease was 0.47.

Disutilities for adverse events

The company did not apply disutilities for adverse events in their base case analysis and assumed these would be captured in the treatment specific utilities. However, they did conduct a scenario analysis that applied disutilities. For anaemia and dyspnoea the literature search did not identify any values in NSCLC so the company used values of -0.09 and -0.048 respectively from Beusterien, et al[59] and from TA420[60].

All other disutility values were valued from Nafees et al[58] or set to zero in the base case.

Age-adjustment

All utility values were age-adjusted in the model as the patient gets older.

ERG comment

The company submission proposes utility values of [redacted] for lorlatinib until progression, 0.72 for PDC until progression and 0.65 thereafter. The ERG proposes that:

- *The progressing disease values reported by Chouaid[57] (0.59 and 0.46) may provide a better reflection of utility across time in the progressed disease state compared to the value reported by Labbe[55], since these values reflect the appropriate number of lines of treatment at entry to the state and following subsequent treatment respectively.*
- *The absolute utility value for progression free on lorlatinib is uncertain as it is based on mapping, and the difference compared to progression free on PDC is also uncertain given a lack of direct comparative evidence at this stage in the pathway.*

5.2.8 Resources and costs

Medicines costs

The license for lorlatinib states that it can be used while clinicians judge there to be a benefit from doing so. This reflects the wording of the license for ceritinib and crizotinib; for alectinib the license specified treatment to progression.

The method used to estimate treatment duration on lorlatinib was to use predicted PFS plus 2.6 months of post-progression treatment, calculated as restricted mean time on treatment minus restricted mean PFS.

The advantages stated for this method were:

- Offers best fit to PFS
- Clinically plausible, in that there are no patients who would be progression-free but 'off treatment'

- The relationship between PFS and time on treatment in Study 1001 is preserved

The company found this to be preferable to fitting parametric curves to data on time on treatment (ToT) with lorlatinib from Study 1001. While reasonable goodness-of-fit to the observed data could be achieved, the functions with better statistical fit either predicted long-term use of lorlatinib which was felt to be clinically implausible (e.g. lognormal), or did not match to the company's preferred extrapolation of PFS and OS, giving clinically implausible results such as patients discontinuing but remaining progression-free (e.g. exponential)
For PDC, the assumed treatment duration was 6 cycles or PFS.

ERG commentary
Treatment beyond progression is a feature of TKI use in ALK+ disease, especially when there are few other effective alternatives to switch to. For example, in the papers for the first meeting of the Appraisal Committee to review brigatinib in 2nd line use, the submission from NHS England states:

> *"5. NHS England also knows that treatment with brigatinib will continue after RECISTdefined disease progression in two main scenarios. The first is when there is a dimensionally small increase in an already small marker lesion: this would trigger definition of disease progression but is clinically irrelevant as the patient remains well; brigatinib would thus continue until there is clinically significant progression ie the development of symptoms. The second is when there is continued systemic response to brigatinib but disease progression in the brain which is then amenable to active treatment with radiotherapy of various types. Treatment would continue until systemic progression or loss of control of the intra-cerebral disease. NHS England considers it likely that the marketing authorisation of brigatinib will recommend use to continue until there is loss of clinical benefit."*

The ERG has clinical advice that the situation with lorlatinib is likely to be similar. However, while it is apparent that there are problems with fitting parametric functions to observed ToT data, the rationale for the method selected is not clear.

An important criterion for ruling out some of the fitted curves was the questionable relationship with predicted PFS, but this assumes the company's preferred curve fit will be accepted. The ERG notes that whilst not providing the best statistical fit, the gamma curve for ToT suffers less from overpredicting than the lognormal, resulting in the ToT converging with PFS just after 10 years when about 3% remain progression free and on treatment. Beyond ten years the gamma ToT curve remains just below the selected PFS curve for the remainder of the model. Thus, the ERG believe it should not be ruled out as viable option.

The ERG's clinical advice is that the use of a targeted therapy may be prolonged when there is no subsequent effective therapy to use. Therefore, it believes the company estimate of [redacted] *in addition to PFS is the minimum and propose a sensitivity analysis adding* [redacted] *and* [redacted] *to PFS. In addition the ERG explores the fitted gamma curve as option for ToT with lorlatinib.*

Administration costs

In the company submission, costs of administration are set out in Table 54 on page 134 of Document B. These include £9.60 per cycle for lorlatinib (based on 12 minutes of hospital pharmacist time) and £174.40 per cycle for all other medicines, except cisplatin (with pemetrexed) which attracts a higher tariff of £374.52 for complex chemotherapy, including longer infusion time.

ERG commentary

From NHS England comment on brigatinib in 2nd line, TA595, papers for Appraisal Committee meeting 1 (page 340 of pdf file):

> *"7. NHS England notes that the drug administration cost per cycle assumed for brigatinib/ceritinib is not the correct one. These drugs are high cost chemotherapy drugs and thus the oral chemotherapy administration tariff should be used. This in 2017/18 is £120."*

In the company submission a sensitivity analysis was provided with the administration cost per cycle for lorlatinib set to £131.61, which seems to more accurately describe NHS England's view.

Subsequent treatments

The company assumed that 60% of patients in the PDC arm would receive subsequent active therapy, in line with clinical consensus reported in atezolizumab combination appraisal (TA584)[29]. With respect to the subsequent treatment distribution following PDC, the company assumed 31% receive atezolizumab and 69% receive pembrolizumab. The assumption that patients would receive one of these immunotherapies following PDC was in line with consensus reported in the FAD for atezolizumab combination (TA584).

Following progression on lorlatinib, 60% of patients were also assumed to have further treatment, with 60% receiving PDC and 40% receiving pemetrexed. This was stated by the company as being consistent with clinical expert opinion.

Finally, in the ABCP comparison provided as an addendum to the CS, the assumption was made that 60% of patients would receive docetaxel upon progression.

ERG commentary

The ERG is satisfied that the modelled subsequent therapies are appropriate and relevant to NHS routine practice. However, the following issues are noted:

1. *The FAD for the atezolizumab combination TA states[29]: "The clinical experts explained that no more than 60% of people would be well enough to have subsequent therapy". It is further noted in the FAD for TA584 that "The committee agreed that the company's revised analysis including 46.6% of people having subsequent therapy after treatment with atezolizumab plus bevacizumab, carboplatin and paclitaxel and pemetrexed plus carboplatin or cisplatin with pemetrexed maintenance was appropriate for decision making. Therefore, the 60% further treatment rate applied may represent an upper bound.*
2. *The proportional distribution of atezolizumab and pembrolizumab following PDC were taken from slide 15 of the public committee slides for TA584 (dated 02 May 2019). The ERGs own clinical expert advised that atezolizumab may be more commonly used in practice*

3. *The ERGs clinical advisor questioned the proportion of patients assumed to receive pemetrexed monotherapy following progressions rather than PDC, which is more effective. There is also a question over potential use of atezolizumab and pembrolizumab following progression on lorlatinib.*
4. *The ERGs clinical advisor questioned the percentage of patients assumed to be suitable for docetaxel following progression on ABCP. The clinicians who contributed to discussions at the committee meeting for the atezolizumab combination appraisal (TA584) seem to have expressed similar reservations: "The clinical experts noted that fewer people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance given that there would be fewer therapeutic options available. They estimated that 30% to 40% of people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel in the larger centres but noted this estimate would be much lower in smaller centres".*

Taken together, these observations suggest potential for the modelling of subsequent treatments to bias cost-effectiveness in favour of lorlatinib. The ERG have carried out further exploratory analysis to assess the sensitivity of results to alternative assumptions.

Other costs

Rates of other resource use associated with health states were estimated by the company using previous STAs in ALK+ NSCLC patients. Costs associated with each resource were derived from the NHS reference costs (2017–2018)[61] and from the Personal Social Services Research Unit (2018).[62] These are summarised in Table 56 of the CS (document B, p.136). Relatively little difference is observed in the total health state costs per patient whether they are in the progression free and progressed disease state, although there are some differences in the frequency of particular elements, depending on which state the patient is in. For example, there is a higher frequency of CT scanning and X rays in the progression free state. Within the economic model the total cumulative health states costs are substantially higher for lorlatinib compared to ABCP or PDC, which is consistent with the improved patient survival.

Costs associated with adverse events were also estimated using previous STAs and NHS reference costs (2017–2018)[61]. These are summarised in Table 58 of CS (document B, p. 140), and the total is applied in the first cycle of the model. The total costs are broadly comparable for lorlatinib and PDC and contribute relatively little to overall costs and expected difference in cost. This is not the case for the ABCP comparator, which has much higher adverse event costs sourced from TA584.[29] A breakdown of this figure is not provided within the appendix to the CS.

Finally, terminal care costs were included as a single period cost in the model and were based on previous NICE appraisals in NSCLC.

The ERG generally agrees with the company's approach to costing in these categories. The source of frequency and cost data is reliable and comprehensive, and the costs have been appropriately incorporated into the economic model.

5.2.9 Cost effectiveness results

The company base case results for lorlatinib versus PDC are provided in section B3.7 of the CS. The results against ABCP were originally provided as an addendum to the CS but were later included as an appendix in an updated submission document (discussed separately below). It should be noted that atezolizumab, bevacizumab and pembrolizumab have PAS discounts in place, which the submitting company does not have access to. Atezolizumab, and bevacizumab form comparators in the ABCP comparison, and atezolizumab and pembrolizumab are included as subsequent treatments in the PDC comparison. Therefore, the company assumed a 30% discount on each of these drugs in their analyses. The ERG has reproduced the company's analyses in a confidential appendix using the actual PAS discounts currently available.

For the PDC comparison, the company provided their base case results using both deterministic and probabilistic analysis. The deterministic ICER came to £50,152 (See Table 63 of the company submission, document B), and the average probabilistic ICER was £46,337 (see Table 64 of the CS, document B). Scatter plots and acceptability curves were also provided in section B3.7 of the CS.

5.2.10 Sensitivity analyses

Further one-way deterministic sensitivity analysis of the PDC comparison revealed the 10 parameters with the greatest impact on the ICER. These included parameters underpinning the calculation of post progression lorlatinib treatment duration, the utility value for progressed disease, and parameters related to subsequent treatment (see Figure 6 of the CS, document B).

A range of further scenario analyses were also provided by the company, which included exploration of the alternative methods for estimating the comparative effectiveness (PFS and OS) of PDC.

The full list of scenarios explored by the company are provided in Table 66 of their submission (document B), and the results are presented in Table 67 of the CS (document B). Of the six methodological approaches for estimating comparative effectiveness of PDC, the ICER for lorlatinib increased most when using the HR from the MAIC of OS in the EXP-3B:5 cohort of Study1001 versus OS in the pooled PROFILE 1001/1005 cohort (method 2). Switching to method 6 for comparative OS (independent OS curve with population adjustment) produced the lowest ICER. Whilst useful for informing the individual impact of changes to the method for estimating comparative OS and PFS, the company did not show the impact of changing the method for both PFS and OS at the same time.

The ICER was also shown to be quite sensitive to the approach used to model time on treatment for lorlatinib, the PFS curve selection for lorlatinib, and the source of post-progression health state utility in the model.

Comparison with atezolizumab in combination with ABCP

In the company submission, the case was made that this comparison is not relevant, based on clinical advice and the lack of data from the Impower150 trial to support use of the ABCP regime in ALK+ patients. However, the company provided a modelled comparison, originally as an addendum to their submission, but later included as an appendix in an updated submission.

The clinical studies used were Study 1001 (cohorts 3B:5) for lorlatinib and the IMpower150 EGRF/ALK cohort for ABCP (n=41). Only 11 of the 41 were noted to be ALK+. The indirect comparison was unanchored and not adjusted for any characteristics that differed.

The same lorlatinib curves selected for the PDC comparison were retained. Published PFS and OS KM curves from the IMpower150 EGRF/ALK cohort were digitised and the IPD were reconstructed. The six standard parametric survival models were then fitted to the PFS and OS outcome data. For consistency with the ABCP appraisal (TA584), and statistical fit based on AIC and BIC, the company selected the exponential curve for OS. For PFS they selected the log-logistic curve which was the ERGs preferred curve fit in TA584. The selected curves are provided in Figure 58 of the CS, Appendix S.

In addition to the independent curve fitting, HRs for PFS and OS were also derived between Study 1001 (EXP-3B:5 cohort) and the ABCP arm of IMpower150 ALK/EGFR subgroup. These were used as an alternative method for estimating the comparative efficacy of ABCP versus lorlatinib. The HRs are presented in Table 13 below. It should be noted that these unadjusted HRs are in favour of ABCP compared to lorlatinib (i.e. higher OS and PFS in the mixed ALK/EGFR subgroup of IMPower). However, the company argue that a population adjustment is required to avoid biasing against lorlatinib.

Table 13 Independent hazard ratio comparing lorlatinib (Study 1001) to ABCP (Impower150 EGFR majority subgroup) (Source: reproduced from Table 69 of the company submission, Appendix S)

	PFS	OS
Study 1001 versus IMpower 150 EGFR+/ALK+ patients	[redacted]	[redacted]

The company apply a 'population adjustment' to reflect the fact that the majority of the relevant sub-group of IMpower150 had EGFR+ disease (n=30) rather than ALK+ disease (n=11). The submission makes the case that prognosis with ALK+ disease is poorer than for EGFR+ disease and hence a failure to adjust could bias the results. To do this, the company compared response to chemotherapy for EGFR+ patients to response to chemotherapy for ALK+ patients. Data used were from the IMPRESS study for EGFR+ patients, and ALUR/ASCEND-5 for PFS and PROFILE 1001/1005[46] for OS in ALK+ patients - in line with the PDC comparison. This gave the results presented in Table 14 below. These HRs were applied to the fitted log-logistic and exponential curves in the EGFR+/ALK+ cohort, to derive curves for an ALK= only population. The company acknowledge the limitation that ALK+ patients made up 27% of the mixed EGFR/ALK cohort, but justify their approach based on the majority being EGFR+ and a lack of alternative data sources. The population adjustments shift both PFS and OS in favour of lorlatinib.

Table 14 HRs for PFS and OS of EGFR+ versus ALK+ patients (Source: reproduced from Table 70 of the company submission, Appendix S)

Analysis	HR
IMPRESS study chemotherapy arm: PFS versus pooled Novello et al[2]. and Shaw et al[3]. chemotherapy data.	[redacted]
IMPRESS study chemotherapy arm: OS versus Ou et al[46]. chemotherapy data.	[redacted]

Other assumptions mainly reflected the comparison with PDC for lorlatinib and the economics model for ABCP used in issuing NICE TA guidance 584[29]. These included:

- Medicines costs – doses from current submission and TA584, prices updated

- Administration of medicines – updated
- Other disease costs – as for current submission
- Adverse event costs – from current submission for lorlatinib, from TA584 for ABCP
- Utility value in PFS – from Study 1001 mapped to EQ-5D in current submission ([redacted]), 0.71 for ABCP (ERG preferred figure in TA584)
- Utility value for PPS – 0.65 from current submission

The company only provided deterministic analysis for the ABCP comparison, and the base case results are reproduced in Table 15 below.

Table 15 Base case results versus ABCP – lorlatinib at PAS price (Source: reproduced from Table 73 of the CS, Appendix S)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£)
ABCP	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,369

ERG commentary

The ERG believe ABCP is a relevant comparator, based on clinical advice. It may only be an option in a minority of cases at this place in the treatment pathway, but these same patients could also receive lorlatinib if it is recommended. It is licensed for ALK+ disease and accepted by NICE, so the company's point about the lack of evidence is not convincing.

The company used the correct clinical studies for the indirect comparison and the ERG agrees that the comparison cannot be anchored. However, there are two contentious aspects to the company's method for indirect comparison:

1. *The decision was not to adjust for differences in prognostic characteristics between the two patient cohorts.*
2. *A population adjustment was made for the difference between EGFR+ and ALK+ cases. The ERG agrees with TA584 that there seems to have been no rationale for the analysis of Impower150 to have combined these two*

mutations together. However, the method used is questionable since it involves comparing the effect of chemotherapy from other clinical studies of EGFR+ and ALK+ patients respectively. Chemotherapy self-evidently has a different mechanism of action to an immunotherapy and it is not clear that the results are relevant to the issue of the relative effectiveness of ABCP in EGFR+ and ALK+ patients. A more direct way would have been to split up the EGFR/ALK combined group: the results for EGFR+ patients have now been published[63].

There are other issues. For example, while it is not explicitly discussed, different utility values appear to be assumed for PFS on lorlatinib and on ABCP. The comparability of these different values is unclear.

5.2.11 Model validation and face validity check

Section B 3.10 of the CS provides details of model validation checks carried out by the company. These included checking the model's predictions of survival against published clinical data, validation by clinical experts, and input data and quality control checks performed by an external organisation.

Validation checks carried out by the company using published clinical data involved comparing the predicted median PFS and OS for lorlatinib and PDC to the observed data. Prediction for lorlatinib were compared to Study 1001. For PDC, ALUR and ASCEND-5 were used to compare PFS, and PROFILE 1001/1005 were used to compare OS. The company states that predictions and observed outcomes were broadly consistent. However, in all cases, the median PFS and OS predictions of the company's model were higher than those observed in clinical studies. For lorlatinib, the model predicted median PFS of [redacted] and median OS of [redacted]. This compared to median PFS of [redacted] and median OS of [redacted] observed in Study 1001. Within Table 67 of the CS, mean PFS and OS predictions from the company's model are also provided, but the equivalent clinical data are not provided. The model predicts an average [redacted] increase in life expectancy with lorlatinib versus PDC.

Although the magnitude of differences in median PFS and OS is not substantial when comparing model predictions to clinical data, the ERG is concerned that the consistent overprediction of survival in the company's model may indicate issues with the extrapolation of the observed data. The CS correctly states that the differences to observed data are proportionally larger in the PDC arm. As such, the overall effect on the ICER of consistently overpredicting PFS and OS for both lorlatinib and PDC cannot be predicted with certainty.

Table 68 in CS (document B, p.154) summarises the validation checks of the model which were carried out with clinical experts. These checks covered many aspects of the model structure and findings. Following submission, the company have subsequently identified an error in Table 68 and clarified that survival curve validation did not take place during the teleconference with clinical experts in September 2018.

Within the CS, validation by clinical experts is particularly emphasised when selecting parametric survival curves within the model. Clinical validation of OS and PFS extrapolations was conducted with two clinical experts in separate teleconferences. The Kaplan-Meier curve was presented to each clinical expert with six survival functions overlaid. A table was also presented which provided the proportion of patients surviving at landmark time points. The clinical experts were then asked, "Based on your experience, which curves best represent overall survival that you would expect to see in this population of patients? Are there distributions you would rule out due to unrealistic predictions?" One clinical expert, with no previous experience of treating patients with lorlatinib, provided a first and second preference for each of the four parametric survival curves (OS and PFS for PDC and lorlatinib). The second clinical expert did not state a preference for OS and PFS for PDC. For lorlatinib, the second clinical expert, who had experience of treating two patients with lorlatinib, validated the choice of a generalised gamma distribution for PFS and preferred the lognormal distribution for OS. In the latter case, the clinical expert focused on the 10-year OS rate, which they estimated to be closer to [redacted] than the [redacted] 10-year survival rate predicted by the exponential distribution. The company's base case extrapolates lorlatinib OS data using the generalised gamma distribution.

Within the company response to clarification questions, it is stated that "Clinicians tended to focus on the proportions alive (or PFS) at each time point and the ordering of curves and this formed the basis for their preference for a curve." However, the ERG notes that there was an error in the table presented to clinical experts which provided landmark values for lorlatinib OS. Specifically, 3-year OS values were erroneously presented under the heading of 5-year OS values. This error applies only to OS for lorlatinib. The correct range of values for lorlatinib 5-year OS is [redacted] rather than the range of [redacted] that was presented to clinical experts. Therefore, based on the landmark values only, the rate decline in OS for lorlatinib between 5 and 10 years appeared much higher than was predicted by each parametric curve. The ERG notes that this error did not extend to the graphical presentation of the data. Given the stated focus on landmark values and the specific focus of one clinical expert on 10-year OS for lorlatinib, it cannot be ruled out that the erroneous presentation of landmark values influenced the clinical validation process. The ERG's clinical adviser was of the opinion that it may be more reasonable to expect 10-year overall survival for lorlatinib to be closer to [redacted] than [redacted].

Table 68 of the CS also states that BresMed Health Solutions carried out checks of data inputted to the model along with general quality control checks. In addition, the ERG checked cell calculations and conducted black box checks of the model using a range of tests suggested by Tappenden and Chilcott (2014)[64]. The results of these checks are reported in Table 15. No major errors or concerns were identified which impact on the deterministic base case analysis within the CS. The ERG notes that a PSA for the ABCP comparator has not been provided by the company.

Table 16 Results of model checks conducted by the ERG

Model component	Model test	Unequivocal criterion for verification	Issues identified in company model
Clinical trajectory	Set relative treatment effect (odds ratios, relative risks or hazard ratios) parameter(s) to 1.0 (including adverse events)	All treatments produce equal estimates of total LYGs and total QALYs	No issues. QALYS not equal due to different progression free utility on PDC/ABCP and lorlatinib.
	Sum expected health state populations at any model timepoint (state transition models)	Total probability equals 1.0	None.
QALY estimation	Set all health utility for living states parameters to 1.0	QALY gains equal LYGs	None.
	Set QALY discount rate to 0	Discounted QALYs = undiscounted QALYs for all treatments	None.
	Set QALY discount rate equal to very large number	QALY gain after time 0 tend towards zero	None
Cost estimation	Set intervention costs to 0	ICER is reduced*	None.
	Increase intervention cost	ICER is increased*	None.
	Set cost discount rate to 0	Discounted costs = undiscounted costs for all treatments	None.
	Set cost discount rate equal to very large number	Costs after time 0 tend towards zero	None.

Model component	**Model test**	**Unequivocal criterion for verification**	**Issues identified in company model**
Input parameters	Produce n samples of model parameter m	Range of sampled parameter values does not violate characteristics of statistical distribution used to describe parameter.	Sample tested for PDC and lorlatinib. No issues. No PSA provided for ABCP comparison.
General	Set all treatment-specific parameters equal for all treatment groups	Costs and QALYs equal for all treatments	For the ABCP comparison, it is not possible to match subsequent treatment costs since 100% of ABCP transition to progressed disease before death. This is not consistent with lorlatinib (and PDC) where a proportion of patients progress directly to death without disease progression (based on Study 1001 data).
	Amend value of each individual model parameter*	ICER is changed	No issues in the company base case.
	Switch all treatment-specific parameter values*	QALYs and costs for each option should be switched	Not tested due to time constraints.

5.3 Exploratory and sensitivity analyses undertaken by the ERG

In addition to the scenario analyses conducted by the company, the ERG conducted some further scenario analyses to explore identified uncertainties in the modelling assumptions.

5.3.1 PDC comparison

For the comparison with PDC, these included the following:

1. Applying each of the alternative five methods for generating comparator PFS and OS curves concordantly. The company scenario analyses applied the alternative methods separately for PFS and OS, which appeared counter to the argument made in the CS that the same method should be used for PFS and OS. The five alternative methods are labelled a)-e) in Table 17
2. Applying iterative upward adjustments to PFS and OS in the PDC arm, to reflect the potential impact of underprediction of these outcomes based on the use of data that did not accurately reflect the modelled comparator; i.e. the PFS and OS data used to inform the PDC arm of the model came from patients treated with singlet chemotherapies or "systemic therapy" that may not adequately reflect the outlook for chemotherapy naïve patients treated with PDC following progression on a second generation ALK inhibitor. The analysis is justified by the ERG's clinical expert advice and reference to Zukin et al, (2013)[65] who reported hazard ratios of 0.46 (95% CI, 0.35 to 0.63) and 0.62 (95% CI, 0.46 to 0.83), for PFS and OS respectively, in a phase III RCT of pemetrexed plus carboplatin versus pemetrexed alone. This was as first-line therapy in patients with advanced NSCLC with an ECOG performance status of 2. Since the exact magnitude of any benefit of PDC over pemetrexed monotherapy is uncertain in the current setting, these exploratory scenarios utilize hazard ratios of: a) 0.9, b) 0.8, c) 0.7, and d) 0.6 to adjust the selected PDC PFS and OS curves upwards (assuming proportional hazards). Each HR is applied to PFS and OS curves simultaneously to avoid the of curves crossing.
3. Applying assumptions to reflect the possibility of treatment effect waning. The company modelling approach results in the hazard of mortality remaining lower in the lorlatinib arm over the entire duration of the model. Given the uncertainties driven by the lack of observed data to validate this assumption,

the ERG explored the impact of setting the mortality rate in the lorlatinib arm equal to that in the PDC arm from a) three years and b) five years in the model. Again, these scenarios were not informed by data, and were conducted purely to assess sensitivity of the results to the assumed ongoing treatment effects.

4. Increasing the estimated mean time on lorlatinib following progression, from [redacted] months in the company base case, to [redacted] and [redacted] to account for fact that clinicians may use the drug for longer following progression in routine practice compared to restricted mean difference observed in Study1001.
5. Exploring the impact of applying the gamma distribution to model ToT for lorlatinib. Whilst not the best statistical fit according to AIC and BIC, it provided more plausible predictions than the exponential curve which the company presented in their sensitivity analysis of this parameter. The gamma ToT curve does not cross the selected PFS curve (also gamma) until about 10 years, when ~3% remain progression free, and it remains below it thereafter.
6. Exploring alternative utility assumptions whereby increments of a) 0.02 and b) 0.08 were added to the selected progression free utility for PDC to represent progression free utility on lorlatinib (covering the range of increments reported by the company from the SLR); c) the value of 0.59 was applied for progressed disease; d) the value of 0.46 was applied for progressed disease; and e) the values in a) and d) were applied in combination (as a lower bound of what may be plausible).
7. Applying alternative assumptions with respect to subsequent treatment costs:
    a. Applying a fixed dosing regimen for pembrolizumab (200mg, every three weeks), rather than the weight-based dosing assumption of 2mg/kg every three weeks for patients who progress on PDC. This was based on advice from the ERG's clinical expert who advised that the fixed dose is more commonly applied in NHS practice.
    b. Increasing the relative proportion of subsequently treated patients who receive atezolizumab rather than pembrolizumab following progression on PDC (to [redacted] versus [redacted], rather than [redacted] versus [redacted] in the CS). This was based on advice from the ERGs clinical expert that atezolizumab may be preferred in this setting on grounds of cost.

c. Applying (a) and (b) in combination
d. Increasing the percentage of patients who progress on lorlatinib who receive PDC to 80%, rather than [redacted] in the company base case. This again was based on the ERGs own expert advice.
e. Reducing the percentage of patients receiving subsequent therapy to 50% following PDC, based on discussions reported in the ACD for TA584 (Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer).

The results of these exploratory analyses are provided in Table 17 using the same comparator drug prices that the company applied in their analyses. In addition to the single scenarios, the ERG considered the following more conservative combination of assumptions: 2b) OS and PFS curves for PDC factored up by applying a hazard ratio of 0.8 to each; 5) gamma distribution for ToT with lorlatinib; 6c) Utility value of 0.59 for progressed disease; 7a) assumed fixed dosing of pembrolizumab at 200mg every three weeks; and 7e) 50% subsequent treatment rate following PDC to reflect diminishing treatment options. The result of this is provided as scenario 8 in Table 17 below.

However, these are not suitable for informing decision making as confidential discounts are available for pembrolizumab and atezolizumab. These analyses are therefore replicated in the confidential comparator PAS (CPAS) appendix using the actual discounts currently available to the NHS.

Table 17 Summary sensitivity analyses undertaken by the ERG

	Description		Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company Base-case			[redacted]	[redacted]	[redacted]	£50,152
1	Alternative PDC PFS and OS survival cure methods	a) Method 1: MAIC HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£45,921
		b) Method 2: MAIC HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£58,747
		c) Method 3: Unadjusted HR EXP-2:3A	[redacted]	[redacted]	[redacted]	£44,104
		d) Method 4: Unadjusted HR EXP-3B:5	[redacted]	[redacted]	[redacted]	£50,282
		e) Method 6: Independent curves & population adjustment	[redacted]	[redacted]	[redacted]	£43,799
2	Hazard ratios for upward adjustments to PFS and OS in the PDC arm	a) 0.9	[redacted]	[redacted]	[redacted]	£50,931
		b) 0.8	[redacted]	[redacted]	[redacted]	£51,943
		c) 0.7	[redacted]	[redacted]	[redacted]	£53,361
		d) 0.6	[redacted]	[redacted]	[redacted]	£55,638
3	Treatment waning	a) Hazard of death on lorlatinib equal to PCD from three years	[redacted]	[redacted]	[redacted]	£56,367
		b) Hazard of death on lorlatinib equal to PCD from five years	[redacted]	[redacted]	[redacted]	£51,600
4	Mean time on lorlatinib following progression	a) [redacted]	[redacted]	[redacted]	[redacted]	£53,938
		b) [redacted]	[redacted]	[redacted]	[redacted]	£59,496

5	Lorlatinib time on treatment	Generalised gamma	[redacted]	[redacted]	[redacted]	£56,876
6	Utilities	a) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.02	[redacted]	[redacted]	[redacted]	£52,642
		b) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.08	[redacted]	[redacted]	[redacted]	£49,382
		c) PD utility is 0.59 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£51,894
		d) PD utility is 0.46 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£56,119
		e) a and d combined	[redacted]	[redacted]	[redacted]	£59,256
7	Subsequent therapies	a) Fixed dose regimen for pembrolizumab	[redacted]	[redacted]	[redacted]	£48,288
		b) proportion of treated patients receiving atezolizumab and pembrolizumab following progression on PDC ([redacted] and [redacted] respectively)	[redacted]	[redacted]	[redacted]	£48,175
		c) a and b combined	[redacted]	[redacted]	[redacted]	£47,338
		d) Proportion of subsequently treated patients who receive PDC and pemetrexed alone following progression on lorlatinib (80% and 20%)	[redacted]	[redacted]	[redacted]	£50,221
		e) 50% receive subsequent therapy following PDC	[redacted]	[redacted]	[redacted]	£51,856
8	Combination	Combines 2b), 5), 6c), 7a), and 7e)	[redacted]	[redacted]	[redacted]	£61,865
		Probabilistic ICER for scenario 8	[redacted]	[redacted]	[redacted]	£59,812

Abbreviations: ERG = Evidence Review Group; EXP = expansion; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; LY = life year; MAIC = match adjusted indirect comparison; NHS = National Health Service; OS = overall survival; PDC = platinum doublet chemotherapy; PFS = progression free survival; QALY = quality-adjusted life year; ToT = time on treatment

5.3.2 ABCP comparison

Similarly, the ERG conducted further exploratory analysis for the ABCP comparison. These included the following:

1. Reducing the magnitude of the population adjustment applied to PFS and OS curves in the ABCP arm. This is because the ALK+ versus EGFR+ population adjustments (applied to the fitted ABCP curves) were derived from unadjusted indirect comparison of ALK+ cohorts exposed to singlet chemotherapy or "systemic therapy", with a cohort of EGFR+ patients treated with cisplatin plus pemetrexed. Since the EGFR+ patients were exposed to a potentially more effective combination chemotherapy, the derived hazard ratios might overestimate the population effects. In addition, the population adjustments were applied to the fitted curves for the mixed IMPower cohort where ALK+ patients already made up 27%. Since there are no data available to better inform the need for population adjustment, the company's log hazard ratios are reduced by a) 25% and b) 50%. (i.e. to 1.33 and 1.53 for PFS and 2.01 and 2.86 for OS respectively).
2. Treatment Waning assumptions. To account for potential diminishing effectiveness over time, these analyses explored the impact of equalizing the hazard of death to that in the ABCP arm from a) year 3 and b) year 5 in the model.
3. Increasing the estimated mean time on lorlatinib following progression, from [redacted] months in the company base case, to [redacted] and [redacted] to account for fact that clinicians may use the drug for longer following progression in routine practice compared to restricted mean difference observed in Study1001.
4. Exploring the impact of applying the gamma distribution to model ToT for lorlatinib. Whilst not the best statistical fit according to AIC and BIC, it provided more plausible predictions than the exponential curve which the company presented in their sensitivity analysis of this parameter. The gamma ToT curve does not cross the selected PFS curve (also gamma) until around 10 years, when ~3% remain progression free, and it remains below it thereafter.
5. Exploring alternative utility assumptions whereby increments of a) 0.02 and b) 0.08 were added to the selected progression free utility for PDC to represent progression free utility on lorlatinib; c) the value of 0.59 was applied for

progressed disease; d) the value of 0.46 was applied for progressed disease; and e) the values in a) and d) were applied in combination (as a lower bound of what may be plausible).

6. Applying alternative assumptions with respect to subsequent treatment costs:
    a. Assuming 80% of subsequently treated patients who progress on lorlatinib receive PDC. This was based on the ERGs own expert advice.
    b. Assuming a lower percentage of patients are suitable for docetaxel following treatment with ABCP (40% rather than [redacted] assumed in the CS). This was based on the ERGs own clinical expert advice and clinical expert advice that was summarised in the ACD for TA584 (Atezolizumab in combination for treating metastatic non-squamous non-small-cell lung cancer): "*The clinical experts noted that fewer people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel compared with pemetrexed plus carboplatin or cisplatin with or without pemetrexed maintenance given that there would be fewer therapeutic options available. They estimated that 30% to 40% of people would have subsequent therapy after atezolizumab plus bevacizumab, carboplatin and paclitaxel in the larger centres but noted this estimate would be much lower in smaller centres*".

The results of these exploratory analyses are presented in Table 18. In addition, a combined scenario included a combination of: 1b) reduced population adjustment log HRs by 50%; 4) generalised gamma for ToT with lorlatinib; 5c) utility value of 0.59 for progressed disease; and 6b) 40% of patients receive subsequent treatment post ABCP. The results are presented as scenario 7 in the Table 18.

As per the PDC comparisons, these analyses are replicated in the CPAS appendix using the confidential discounted prices available to the NHS for atezolizumab and bevacizumab.

Table 18 Summary sensitivity analyses undertaken by the ERG

	Description		Incremental costs	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Company Base-case			[redacted]	[redacted]	[redacted]	£27,369
1	Reducing population adjustment hazard ratios (on log scale)	a) By 25% (HR for PFS = 1.53; HR for OS = 2.86)	[redacted]	[redacted]	[redacted]	£26,857
		b) By 50% (HR for PFS = 1.33; HR for OS = 2.01)	[redacted]	[redacted]	[redacted]	£28,869
2	Treatment waning	a) Hazard of death on lorlatinib equal to ABCP from three years	[redacted]	[redacted]	[redacted]	£22,187
		b) Hazard of death on lorlatinib equal to ABCP from five years	[redacted]	[redacted]	[redacted]	£22,867
3	Mean time on lorlatinib following progression	a) [redacted]	[redacted]	[redacted]	[redacted]	£31,505
		b) [redacted]	[redacted]	[redacted]	[redacted]	£37,577
4	Lorlatinib time on treatment	Generalised gamma curve	[redacted]	[redacted]	[redacted]	£34,715
5	Utilities	a) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.02	[redacted]	[redacted]	[redacted]	£28,861
		b) PF utility on lorlatinib = PF utility on PDC (0.72) + 0.08	[redacted]	[redacted]	[redacted]	£26,911
		c) PD utility is 0.59 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£28,691
		d) PD utility is 0.46 (Chouaid et al)	[redacted]	[redacted]	[redacted]	£32,043

		e) a and d combined	[redacted]	[redacted]	[redacted]	£34,107
6	Subsequent therapies	a) 80% of subsequently treated patients who progress on lorlatinib receive PDC	[redacted]	[redacted]	[redacted]	£27,445
		b) 40% receive subsequent treatment with docetaxel following progression on ABCP	[redacted]	[redacted]	[redacted]	£27,561
7	Combination	Combines 1b), 4), 5c), and 6b),	[redacted]	[redacted]	[redacted]	£44,692

5.4 Conclusions of the cost effectiveness section

5.4.1 Summary

Based on the remaining uncertainties in the economic model, and lack of appropriate data to inform the comparative effectiveness of lorlatinib versus PDC and ABCP, the ERG finds it difficult to draw conclusions with respect to the most plausible set of assumptions to apply in the economic model. Therefore, the ERG suggests that the following issues relating to cost-effectiveness be raised in the technical report for consultation:

Issue 1

The design of Study 1001, as a non-comparative single-arm study, means there is substantial uncertainty in estimating the lifetime clinical effectiveness of lorlatinib in its licensed indication. While the company has undertaken an indirect comparison to address this, there are several issues and much of the uncertainty remains. Issues include:

- The selection of clinical studies to represent the PDC treatment arm
- The selection of the method to carry out the indirect comparison
- The most plausible projections of PFS and OS for lorlatinib
- The most plausible projections of ToT, particularly with respect to treatment post-radiographic progression treatment duration.

Issue 2

The utility values selected are open to question:

- The selected value for the progressed disease state appears high compared to other published values specific to treatment line.
- There is a lack of direct comparative evidence for the applied difference in PF utility on lorlatinib versus PF utility on PDC (the same point applies in the comparison with ABCP). The magnitude of any applied difference is therefore uncertain.

Issue 3

The treatment duration calculation for lorlatinib is broadly plausible but may underestimate the extent to which clinicians tend to prolong treatment following radiographic progression in routine practice when there are no other effective treatment options available.

Issue 4

Assumptions about proportion of patients receiving subsequent therapies following the intervention and comparator treatments, and the distribution of these subsequent therapies is uncertain and could benefit from further clinical input.

6 End of life

The company case against PDC appears consistent with the NICE criteria for consideration as an end of life treatment. Average life expectancy is well below 2 years on PDC in the company base case ([redacted]) and remains below this value across the scenarios assessed. Despite the limitations in the comparative evidence base, it is plausible to the ERG that treatment with lorlatinib will result in a gain in life expectancy of more than three months.

The same is true of the company base comparison against ABCP ([redacted]), but the average life expectancy on ABCP is dependent on the uncertain population adjustment that is applied to the fitted curve. However, it remains below 2 years as long as the log HR for the population adjustment of OS is not reduced by 55% or more (i.e. from a HR value of [redacted]). The survival gain remains above three months across all scenarios assessed.

7 Overall conclusions

The current submission focuses on adult patients with metastatic (stage IV) ALK-positive NSCLC. Overall, the company's review process for the selection and assessment of the clinical effectiveness evidence was appropriate. While the ERG agree that Study 1001 is the current best source of effectiveness evidence for lorlatinib, they are concerned about the limitation of the current evidence-base, only a small (n = 139) single arm study.

The comparator addressed in the CS is limited to pemetrexed with cisplatin/carboplatin (PDC). The company did not consider atezolizumab with bevacizumab, paclitaxel and carboplatin (ABCP) a relevant comparator.

There is evidence to suggest lorlatinib provides a response in the target group of patients and has an impact on progression free and overall survival. The company present a matched adjusted indirect comparison to compare lorlatinib to chemotherapy, which indicates a survival benefit with lorlatinib over chemotherapy. However, as described in chapter 4, the ERG are apprehensive over the validity of the results in the MAIC due to concern over the relevance of the comparator data sources used.

The considerable uncertainties with respect to the comparative effectiveness of lorlatinib versus PDC and ABCP requires many assumptions to be made in the economic modelling and makes it difficult to establish the most plausible ICER. The ERG has conducted further scenarios analyses which lead to both upward and downward uncertainty in the ICERs versus PDC and ABCP.

The ERG is of the opinion that the evidence for lorlatinib is limited and future research should consider a head to head trial of lorlatinib against relevant comparators at the correct place in the treatment pathway.

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