NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Contents:

The following documents are made available to consultees and commentators:

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

2. **Comments on the Appraisal Consultation Document from Pfizer**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. ALK Positive
   b. Takeda

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

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

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Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 2 March 2023. Please submit via NICE Docs.

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

Comment number	Comments

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1

The updated cost-effectiveness model aligns with the majority of the committee's preferred assumptions

We are submitting an updated base-case to reflect the outcomes of the committee meeting on 19th January. Please see changes to the company base-case to align with the committee's preferred assumptions summarised in the table below. Assumptions in bold demonstrate where we have not aligned the base-case with the committee's preferred assumptions, or made amends to the assumption, with justifications provided in our responses below. Updated results are provided in comment 8.

Assumption	Committee preferred assumption	Company base case after technical engagement	Updated company base case	ICER impact
Health states	Removal of CNS PD health state	Inclusion of CNS PD health state	**Inclusion of CNS PD health state (see comment number 5)**	**Large**
Utilities	TA670 utilities	CROWN utilities	TA670 utilities	Large
Drug acquisition costs	Use RDI costing method for all treatments including lorlatinib	Detailed dosing for lorlatinib from CROWN	**Detailed dosing for lorlatinib from CROWN (see comment number 7)**	**Large**
PFS NMA	ALESIA included	ALESIA excluded	ALESIA included	Small
Treatment effect cap	10 years	N/a	10 years	Small
Treatment beyond progression	Include 5.7 months of treatment beyond progression for both first-line and second-line lorlatinib in the base-case analysis, and use the EAG's estimate for the proportion of people progressing to second-line lorlatinib	Scenarios presented for treatment beyond progression after first- and second-line lorlatinib	Align with committee's preferred assumptions, also include **3 months treatment beyond progression for first-line alectinib and brigatinib and proportion aligned with EAG (see comment number 6)**	Small
Adverse event disutility	CROWN durations for AE	CROWN durations presented as scenario only	CROWN durations for AE	Small
PFS	Model arm-specific death as a proportion of PFS	Deaths calculated as a proportion of PFS events across both arms	Model arm-specific death as a proportion of PFS	Small
PPS	The committee noted the high uncertainty associated with the company's modelling of PPS, but recognised the limitations of the evidence	Study 1001 (PPS for patients receiving lorlatinib), and PROFILE 1005 (PPS for patients receiving chemotherapy)	Explored alternative data sources but presented justification for Study 1001 and PROFILE 1005.	Small

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2	***Budget impact resulting in low risk of decision error*** The consequence of decision error is low given the limited budget impact estimated within this appraisal and the existing indication for previously treated ALK-positive advanced NSCLC (TA628) to which it will also apply. In addition, immediate cost-savings to the NHS are anticipated from the updated PAS offer for lorlatinib. [redacted] ***ORBIS designation*** Lorlatinib has ORBIS designation as an innovative product and offers the potential for substantially improved outcomes over alectinib and brigatinib. This level of innovation is reflected in the fact that whilst there is currently substantial uncertainty within the PFS, IC-progression and OS estimates from CROWN, these are not primarily due to limited follow-up, but due to the performance of lorlatinib. ***Cancer Drugs Fund*** Ongoing data collection from CROWN (further data cuts are planned in 2025 and 2028) is anticipated to address several key uncertainties including long-term PFS, the transition due to intracranial time to progression (IC-TTP) and the OS benefit for lorlatinib. In addition, the initial model structure, which uses OS data from CROWN from the March 2020 data-cut, demonstrates the potential for lorlatinib to be plausibly cost-effective.
3	**Section 3.6** ***Uncertainty in PFS*** The committee have highlighted areas of substantial uncertainty in the CROWN data, with median PFS not yet being met. As highlighted by clinicians present in the committee meeting, this represents a strength of the CROWN data, and PFS of 2-3 years is considered to be clinically meaningful by the clinicians present in the committee meeting on the 19th January 2023. The model predicts a median PFS for lorlatinib of 53.2 months, based on the most conservative but most clinically plausible survival extrapolation (exponential). This aligns with clinical expectations of median PFS (4-5 years) from a global advisory board, and is substantially higher than median investigator-assessed PFS reported for alectinib and brigatinib (34.8 and 30.8 months, respectively). ***PFS for lorlatinib is significantly greater than currently available treatments*** We acknowledge that parts of the dataset are immature and may lead to uncertainty, including the median PFS for lorlatinib in the CROWN study. However, there is little uncertainty that lorlatinib improves the amount of time people have before their condition progresses compared to alectinib and brigatinib. For CROWN and ALTA-1L, the primary endpoint was PFS by BICR. The hazard ratios across the 3 studies for this endpoint are as follows: CROWN: 0.27 (0.18-0.39); ALEX 0.50 (0.36 – 0.70); ALTA-1L 0.48 (0.35 – 0.66). For ALEX, the primary endpoint was PFS assessed by investigator. The hazard ratios across the 3 studies for this endpoint are as follows: CROWN 0.19 (0.13 – 0.27); ALEX 0.43 (0.32 – 0.58); ALTA-1L 0.43 (0.31 – 0.58). The results of these primary endpoints provide clarity, not uncertainty, that lorlatinib improves the amount of time people have before their condition progresses compared to alectinib and brigatinib. The dataset also provides clarity with regard to the progression free survival rate at the 12-, 24-, and 36-month timepoints. At each timepoint, a higher proportion of people have not progressed on lorlatinib, when compared to alectinib and brigatinib. The 36-month data, as assessed by investigator is as follows:

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	<table><tr><th></th><th>CROWN (lorlatinib)</th><th>ALEX (alectinib)</th><th>ALTA-1L (brigatinib)</th></tr><tr><td>PFS Rate at 36 months (95% CI), % of patients</td><td>63 (54-71)</td><td>46 (NA)</td><td>45 (36-54)</td></tr><tr><td>PFS HR versus crizotinib (95% CI)</td><td>0.27 (0.19-0.39)</td><td>0.50 (0.36 – 0.70)</td><td>0.48 (0.35 – 0.66)</td></tr><tr><td>Median PFS (BICR)</td><td>NR</td><td>25.7 months</td><td>24.0 months</td></tr><tr><td>Median PFS (INV)</td><td>NR</td><td>34.8 months</td><td>30.8 months</td></tr></table> Clinical and patient experts confirmed in the ACM on the 19th January that PFS is clinically relevant and important for patients. Despite a more mature dataset in terms of median follow up, lorlatinib is outperforming both alectinib and brigatinib in PFS as described above, and the only uncertainty is the total additional duration of time people may have if receiving treatment with lorlatinib.
4	**Section 3.6 (uncertainty in overall survival)** ***Early data shows lorlatinib reduces the risk of death compared with crizotinib*** At the March 2020 CROWN data cut-off, the majority of patients in both treatment arms were still alive. The HR for OS showed a 28% reduction in the risk of death in the lorlatinib arm compared with the crizotinib arm (HR=0.72 [95% CI: 0.41, 1.25]). Deaths had occurred in 15.4% and 19.0% of patients in the lorlatinib and crizotinib arms, respectively. The median OS was not estimable (NE) in either treatment arm. ***With more mature OS data from 2025, lorlatinib has plausible potential to cost-effectiveness*** The original company model submitted in May 2022 utilised OS data from CROWN, before an updated model utilising PPS data from Study 1001 / PROFILE 1005 was submitted following the EAG's concerns at the clarification question stage about the immaturity of the OS data. If a CDF recommendation were made for lorlatinib, then a re-submission for routine commissioning would use the original model structure with more mature OS data, which is expected to be available in 2025. At the current PAS and using the original model structure, the model demonstrates that lorlatinib has the plausible potential to be cost-effective.
5	**Section 3.6 and 3.13 (modelling CNS PD health state)** In response to the committee's preference to using the 3-health state model, we would like to provide additional clarity on the model structure (given the change in structure after clarification questions), and the data from CROWN, PROFILE 1005 (2L chemotherapy) and Study 1001 (2L lorlatinib) used to populate the 4-state model, depicted in Figure 1 below. ***Sufficient data from CROWN are available to inform model transitions to enable benefits of lorlatinib in delaying CNS progression to be reflected*** Overall PD and intracranial PD were independent events and were assessed by BICR and IC-BICR, respectively. Intracranial-time to progression (IC-TTP) simply considered the time of IC PD. Based on section 5.4.3, the investigator could decide to continue with study treatment even in case of overall PD and specifically in case of intracranial response, as reported in Section 5.4.3 of the study protocol: *5.4.3. Treatment Duration* *Treatment will continue until confirmation of disease progression, patient refusal, or unacceptable toxicity, whichever occurs first. Once the patient has documented PD by BICR, patients should be discontinued from study treatment. However, if according to the Investigator's clinical judgment, a*

patient with evidence of PD is still experiencing clinical benefit, the patient may be eligible for continued treatment with the assigned study drug after discussion between the Investigator and Pfizer. The Investigator's judgment should be based on the overall benefit/risk assessment (eg, intracranial response), and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data. In that case, the patient must undergo the same assessments foreseen during the active treatment period. As far as tumor assessments:

•If only extracranial progression was documented, with intracranial lesions stable or in response, intracranial assessments should be performed until intracranial PD;
•Once intracranial PD is documented no further tumor assessments are required

Only 9 lorlatinib patients (6%) had an IC-progression after 36-months of follow up in CROWN. Of these, [redacted] patients had an IC-progression at least 7 days after overall PD/death (see table below). This additional data table is presented to address the EAG and committee concern it was not clear if appropriate data was captured in CROWN because people with non-CNS progression events appeared to have been censored from subsequent analysis, and that everyone who had a CNS progression event after progression by any other definition were excluded (in Section 3.6 of the draft guidance). Whilst tumour assessment stopped for patients who experienced a progression and initiated a subsequent therapy, data are available for patients who had an IC-progression following an extracranial progression, and the data are presented below:

After 36.7 months follow-up, only 6% of lorlatinib patients, compared to 34.7% of crizotinib patients had experience IC-progression (HR 0.08, 95% CI 0.040-0.174), and therefore it is important that this substantial benefit to patients is captured in the model. Additional data will be collected in the ongoing CROWN trial.

Figure 1. Model structure

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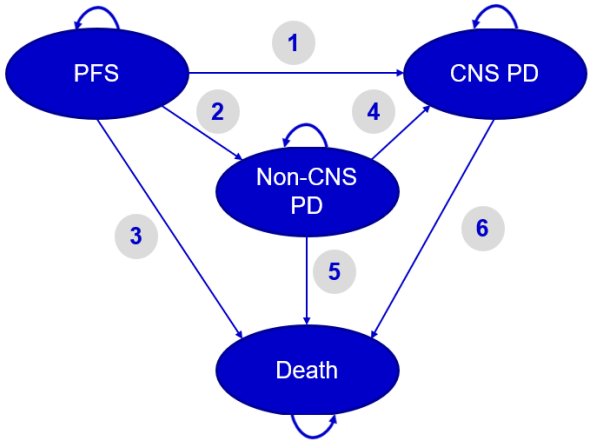


Transition	Data source	Definition	Lorlatinib (n=149) patients with event, n (%)	Crizotinib (n=147) patients with event, n (%)	HR (95% CI)
1	CROWN	IC-TTP	9 (6.0)	51 (34.7)	0.08 (0.040-0.174)
2	CROWN	Extracranial progression	49 (32.9)	92 (62.6)	0.27 (0.184-0.388)
3	CROWN	Progression events which were death	11 (22.5)	4 (4.3)	N/a
4	CROWN	IC-PD after overall EC-PD	[redacted]	[redacted]	N/a
Transition	**Data source**	**Definition**	**Median PPS post lorlatinib (chemotherapy)**	**Median PPS post alectinib / brigatinib (2L lorlatinib)**	**HR (95% CI)**
5	PROFILE 1005/ Study 1001	Overall survival after 1L treatment	5.9 months	20.7 months	N/a
6	PROFILE 1005/ Study 1001		5.9 months	20.7 months	N/a

The company and EAG agreed in technical engagement that the most appropriate data sources were used to model PPS for both CNS and non-CNS PD, and this has been validated by an additional literature search

The committee highlighted concern about the suitability of the PROFILE 1005 and Study 1001 trials used to model post-progression survival (PPS). Due to the concerns highlighted by the EAG about the immaturity of OS data in CROWN to populate the original economic model submitted in May 2022, an alternative approach was taken using OS data from second-line trials to model PPS.

During technical engagement, it was confirmed between the EAG and the company that PROFILE 1005 and Study 1001 were the most appropriate data to use, as accepted in TA628. In Study 1001, 39/69 (57%) of patients had brain metastases at baseline – a higher proportion than in CROWN. The EAG noted that *"The prognosis of people with intracranial metastases may be worse than the general population with progressed disease, so using PPS outcomes from a population with a better*

prognosis may overestimate the benefit gain in people with CNS PD." However, as lorlatinib demonstrates efficacy in preventing CNS metastases, the model does not fully capture the PPS benefit for 1L lorlatinib.

To ensure the most relevant data to inform PPS was used in the model, a targeted literature search for post-progression survival data has been conducted, from which two potential alternative studies were identified and assessed:

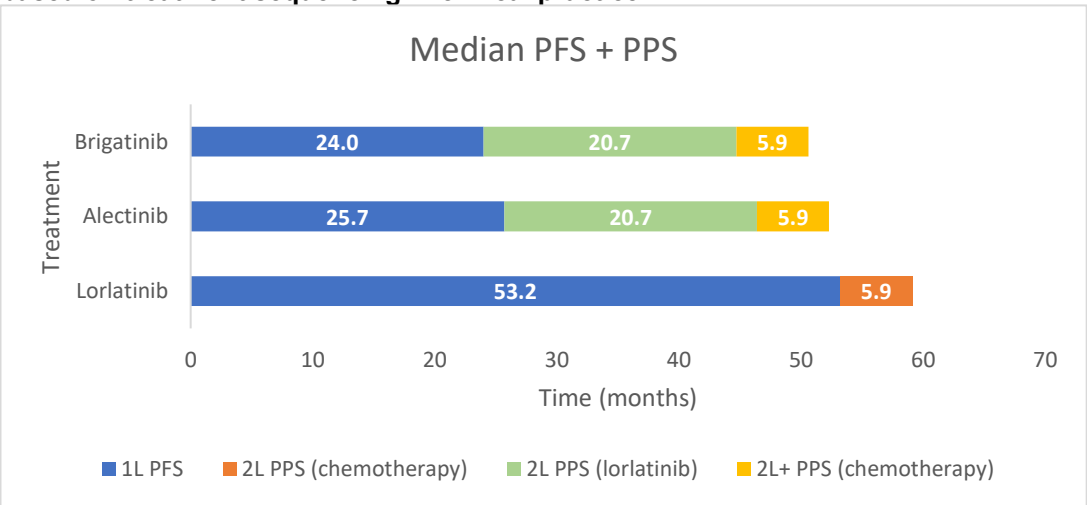
1. *Efficacy of platinum/pemetrexed combination chemotherapy in ALK-positive NSCLC refractory to second-generation ALK inhibitors.*[1] This was a retrospective study of 58 patients. 26% of patients had brain metastases at baseline, 64% of patients had no brain metastases at baseline, and 10% were not assessed. Most patients (88%) had received at least 2 prior ALK TKIs, and twelve patients (21%) received three or more prior ALK TKIs. Based on the number of lines of prior treatment received, this study is less relevant than Study 1001 to model PPS.

2. *Atezolizumab for First-Line Treatment of metastatic non-squamous NSCLC.*[2] This was a study of patients with any PD-L1 immunohistochemistry status, however patients with EGFR or ALK genomic alterations were included if they had had disease progression with or unacceptable side effects from treatment with at least one approved TKI inhibitor. Patients were randomized to atezolizumab plus BCP (ABCP) or bevacizumab plus carboplatin plus paclitaxel (BCP). 3.2% and 5.2% of patients in the ABCP and BCP groups respectively had positive ALK rearrangement status. Based on the small number of ALK patients enrolled in the study, this trial is considered less representative to model PPS.

Number of prior ALK TKIs (%)	Study 1001	PROFILE 1005	Lin (2020)	Socinski (2018)
1	28 (20)	NR	7 (12)	NR
2	111 (80)	NR	39 (67)	NR
≥3		NR	12 (21)	NR

The PPS model results in survival estimates for the three treatments addressed in the decision problem as depicted in the figure below:

Figure 2. Comparison of median PFS + PPS for ALK TKIs (alectinib, brigatinib and lorlatinib) based on treatment sequencing in clinical practice



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	In addition to increased overall time in the PFS and PPS health states, lorlatinib delays the amount of time until patients receive chemotherapy, which was reported by the patient representatives present in the ACM on the 19th January to be clinically meaningful for patients.
6	**Section 3.15 (modelling treatment beyond progression)** The committee's preferred assumption includes 5.7 months treatment beyond progression for lorlatinib in first- and second-line, based on second-line data, as no first-line data are available. Treatment beyond progression reflects the use of lorlatinib in UK clinical practice in delaying time until patients receive chemotherapy. As highlighted by the clinicians present in the ACM on 19th January, it is expected that patients receiving first-line alectinib or brigatinib will also continue to be treated beyond progression. Therefore, the assumption of an additional 3 months of treatment beyond progression has also been incorporated into the company's updated base case for alectinib and brigatinib. The 3 month duration was suggested by clinical experts in the ACM on the 19th January.
7	**Section 3.18 (Dosing)** As highlighted in the technical engagement response, 100 mg starting dose is considered to be more accurate, with all patients starting on 100 mg pack and dose reductions occurring at the end of a cycle, if required. As confirmed by clinicians present in the first ACM on 19th January, the assumption of all patients starting on 100 mg is reflective of clinical practice in the UK. Therefore, there is no need to use the simplified (and less accurate) methodology of RDI, when we have data for detailed dosing, it is more reflective of clinical practice, aligned with clinician opinion and the model can incorporate it accurately.
8	**Updated cost-effectiveness results with [redacted] lorlatinib PAS:** Updated base-case:

Treatment	**Total costs**	**Total LYs**	**Total QALYs**	**Incremental costs**	**Incremental LYs**	**Incremental QALYs**	**ICER**
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Treatment	**Total costs**	**Total LYs**	**Total QALYs**	**Incremental costs**	**Incremental LYs**	**Incremental QALYs**	**ICER**
Brigatinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

In the original model, which utilises immature OS data from CROWN, lorlatinib also demonstrates plausible cost-effectiveness at a [redacted] PAS:

Treatment	**Total costs**	**Total LYs**	**Total QALYs**	**Incremental costs**	**Incremental LYs**	**Incremental QALYs**	**ICER**
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

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Treatment	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Brigatinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is 'commercial in confidence' in turquoise and information that is 'academic in confidence' in yellow. If confidential information is submitted, please submit a second version of your comments form with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the NICE Health Technology Evaluation Manual (section 5.4) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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

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2. Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *New England Journal of Medicine*. 2018;378(24):2288-2301.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	ALK Positive UK]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

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Example 1	We are concerned that this recommendation may imply that …….. We are concerned that this recommendation may imply that there are no benefits to Lorlatinib being used in the first line setting.
1	Patients presenting with multiple brain metastases may benefit from a TKI with the highest brain penetration and currently don't have that option.
2	We would like to see Lorlatinib available for the 1st line ttherapy as well as its current position – second line.

Insert extra rows as needed

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Comment number	Comments Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	• *Has all of the relevant evidence been taken into account?* Yes. • *Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?* Yes, however please note our comments below. • *Are the provisional recommendations sound and a suitable basis for guidance to the NHS?* Yes. • *NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others.* We see no issues here with the preliminary recommendations.
2	We believe the following description of the patient expert's side effects on anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor (TKI) treatment misrepresents the patient expert's comments during the Committee meeting: Page 6: "*The patient experts commented that some people find that lorlatinib has fewer side effects than other ALK TKIs. For example, they have had less fatigue and a better quality of life than they did when taking either alectinib or brigatinib.*" We understand from the patient expert's comments during the Committee meeting that they received treatment with alectinib, which was associated with fatigue, followed by lorlatinib. It is therefore an inaccurate representation of the patient expert's comments to refer to brigatinib in this statement, given they did not mention any previous treatment with brigatinib. The following description of side effect profiles from Page 14 is a more accurate representation of the Committee meeting discussion, so we propose that the mention of brigatinib is removed from Page 6 and instead aligned with the below: Page 14: "*The patient experts explained that some side effects associated with alectinib are not found with lorlatinib. People taking lorlatinib may have less fatigue compared with other ALK TKIs.*"
3	We would like to flag a factual inaccuracy in the following statement: Page 8: "*The committee noted that the proportion of people with an ECOG of 0 or 1 in clinical trials of alectinib (ALTA-1L) and brigatinib (ALEX) was very similar to that in CROWN.*" ALTA-1L is the clinical trial for brigatinib, whereas ALEX is the clinical trial for alectinib. The references to the clinical trial should therefore be swapped in the above statement.
4	We agree with the Committee and EAG's position that a comparative analysis of Grade 3 and 4 adverse events (AEs) would help in decision-making, and would provide insight into the "*trade-off between the likely better progression-free survival outcomes with lorlatinib (that might or might not translate into better overall survival), and the different safety profiles of alectinib and brigatinib*." (Page 14, Draft Guidance). As well as the clinical implications of the lorlatinib AE profile, we would like to encourage the Committee and EAG to consider the cost implications of lorlatinib-associated AEs. Page 95 of the Company submission notes that "*Grade 3 or higher all-cause AEs that were observed in at least 5% of patients were considered in the model*". Table 64 of the Company submission lists the AEs included, and costs per event. We note that there are no cognitive AEs listed in Table 64, despite

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Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on 2 March 2023. Please submit via NICE Docs.

	clinical experts from the Committee meeting highlighting central nervous system (CNS) toxicity as a unique aspect of managing patients on lorlatinib. Due to redactions within the Company submission, rates of AEs are not visible, so it is unclear if all relevant AEs have been appropriately costed for. We would encourage the Committee and EAG to consider the clinical and cost implications of Grade 3/4 AEs, and any impact this could have on cost-effectiveness estimates for lorlatinib vs the comparators.

Insert extra rows as needed

Checklist for submitting comments

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

Single Technology Appraisal (STA)

Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer [ID3896]

EAG Addendum: Review of the company's response to consultation on the draft guidance document

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

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None.

Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

Note on the text

All commercial-in-confidence (CIC) data have been highlighted in blue and underlined, and all academic-in-confidence (AIC) data are highlighted in yellow and underlined.

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1 OVERVIEW

The External Assessment Group (EAG) was requested by NICE to provide validity checks on the additional evidence submitted by the company in response to the consultation on the draft guidance document (DGD) and to identify any areas of remaining uncertainty. Due to the limited time available, the additional work undertaken by the EAG does not constitute a formal critique of the company's resubmission and hence does not accord with the procedures and templates applied to the original submission. Specifically, the EAG has not fully validated several changes to the model outlined in the company's response to the DGD. Instead, the EAG has conducted high-level checks of these proposed changes and ensured replicability of the results presented by the company.

The company's response to the DGD comprises seven comments summarised in Table 1, and presents a revised base case that accepts and adopts several of the committee's preferred assumptions. The company contests several of the committee's preferences as stated in the DGD, including the preferred removal of the CNS PD health state. The company's responses to each of the issues are discussed in Section 2, while Section 3 presents an overview of the company's revised base case and the updated EAG base case. The key driver of incremental costs in the company's analysis was the incorrect implementation of treatment beyond progression for alectinib and brigatinib. This is discussed in Section 2.6.

Table 1 Summary of the company's comments on the DGD

Comment	
1	The updated cost-effectiveness model aligns with the majority of the committee's preferred assumptions
2	Budget impact resulting in low risk of decision error
3	Uncertainty in progression-free survival (DGD Section 3.6)
4	Uncertainty in overall survival (DGD Section 3.6)
5	Modelling CNS PD health state (DGD Section 3.6 and 3.13)
6	Modelling treatment beyond progression (DGD Section 3.15)
7	Dosing (DGD Section 3.18)

2 DESCRIPTION AND CRITIQUE OF RESPONSE

2.1 Comment 1: The updated cost-effectiveness model aligns with the majority of the committee's preferred assumptions

The company provide a table in which the assumptions adopted in their updated base-case analysis are compared to the committee's preferred assumptions following ACM1. The company's updated base-case analysis now reflects the following committee's preferences in full:

- Utilities: TA670 utilities implemented
- PFS NMA: ALESIA included
- Treatment effect cap: 10 years
- PFS: Trial arm-specific deaths as a proportion of progression events

The company adopted the committee's preferences in part on the following issues:

- Treatment beyond progression: Aligned with committee's preferred assumptions but also include 3 months treatment beyond progression for first-line alectinib and brigatinib, proportions aligned with EAG.
- Adverse event disutility: CROWN AE durations (Committee-preferred disutility magnitudes not applied)
- PPS: Alternatives presented but maintained Study 1001 and PROFILE 1005

The company's updated base case did not adopt the committee's preference for the removal of the CNS PD health state. The company also maintains the use of detailed dosing information to calculate drug acquisition costs for lorlatinib, whereas the committee preferred a consistent approach for all comparators using RDI.

2.2 Comment 2: Budget impact resulting in low risk of decision error

The company consider the consequence of decision error to be low given the limited budget impact associated with first-line lorlatinib use in this indication. In their DGD response, the company present an updated PAS offer for lorlatinib, [redacted]

The company suggest that forthcoming data cuts from CROWN will address key uncertainties such as the lack of long-term data on PFS, intracranial progression, and OS.

2.2.1 The EAG's response

The committee concluded that all presented ICERs were above the range considered an acceptable use of NHS resources. The wider budgetary consequences of a positive recommendation for lorlatinib in this position would not mitigate decision error because they assume a usage pattern of second-line lorlatinib which is inconsistent with the recommendation at first-line. That is, the above cost-savings would only be realised if first-line use of lorlatinib was independent of uptake at second-line.

Moreover, the budget impact of the decision is not a factor directly considered by the committee. Lorlatinib must demonstrate plausible potential for cost-effectiveness in the indication considered in the current appraisal to be made available through the Cancer Drugs Fund.

2.3 Comment 3: Uncertainty in progression-free survival (DGD Section 3.6)

The company acknowledge the substantial uncertainty around PFS on lorlatinib arising from the immaturity of this outcome in CROWN. The company reiterate that, based on the NMA results, lorlatinib generates a statistically significant improvement in PFS outcomes compared to alectinib and brigatinib, and stated that the only uncertainty is the magnitude of PFS benefit over the comparators.

2.3.1 The EAG's response

The EAG agrees that the available data support improved PFS on lorlatinib relative to alectinib and brigatinib. The magnitude of this benefit remains uncertain, and is likely to become clearer with further data cuts from CROWN.

2.4 Comment 4: Uncertainty in overall survival (DGD Section 3.6)

The company state that currently available OS data from CROWN are suggestive of a reduction in the risk of death in the lorlatinib arm compared with the crizotinib arm. The company also suggest that a re-submission for routine commissioning following a period of access to lorlatinib through the CDF would allow more mature OS data from the CROWN trial to be included.

The company suggest that more mature OS data could be used in the original model structure to demonstrate cost-effectiveness. It is also suggested that using the current PAS in the original model structure, it is demonstrated that lorlatinib has the plausible potential to be cost-effective.

2.4.1 The EAG's response

The EAG notes that the original DGD describes the EAG's position as follows: "…there was no evidence that the increased progression-free survival would lead to increased overall survival benefit." The EAG disagrees with this representation of its position. Whilst the CROWN study does not demonstrate a genuine OS benefit at this stage, the modelled OS benefit is driven directly by extrapolation of available PFS data.

It is not unreasonable to assume that on the basis of a significant extension to PFS, an extension to OS would follow. Indeed, the clinicians at the first ACM supported the clinical plausibility of independence of post-progression survival outcomes from previously received therapies. That is, a patient's prognosis would remain the same regardless of what treatment they were on prior to the point of progression. Even with the application of a cap at ten years on the duration of the treatment

effect of lorlatinib on PFS, the additional time patients are expected to remain event-free produces a significant survival benefit versus the comparators.

As discussed in the EAG Report, the implausibly long post-progression survival observed on crizotinib in CROWN, which is likely to be driven by unrepresentative use of further treatment lines following progression, means there are as yet very few OS events in either treatment arm. Beyond the point of progression in CROWN, outcomes on crizotinib are unlikely to represent a viable source of data with which to inform the model in future, due to the confounding effect of subsequent therapies.

The EAG must also emphasise that the original model structure does not represent a plausible alternative approach to modelling OS. The original model structure would not be accepted in any future re-submission.

2.5 Comment 5: Modelling CNS PD health state (DGD Section 3.6 and 3.13)

The company reiterate their preference for using a four-state model in order to capture the benefits of lorlatinib on intracranial outcomes. The company provide data to support the position that important information about IC progression events occurring secondary to development of PD in CROWN was not lost due to censoring. Only [redacted] patients on lorlatinib had an IC progression event >7 days after overall PD. The company again state that it is important that this substantial benefit of lorlatinib is captured in the model.

Alternative sources of PPS data

The company identified two potentially relevant studies to inform post-progression survival in the model.

The first was a retrospective study of 58 patients which assessed the efficacy of platinum + pemetrexed combination chemotherapy in patients refractory to second generation ALK inhibitors. However, 88% of included patients had received at least two prior ALK TKIs, with 21% receiving three or more prior TKIs, the company considered this study less relevant to inform PPS on chemotherapy.

The second study assessed the use of atezolizumab for first-line treatment of metastatic ns-NSCLC compared to bevacizumab plus carboplatin plus paclitaxel. As only 3.2% and 5.2% of included patients had an ALK rearrangement, the company considered this trial less representative than those already in use.

The company implemented a scenario which used data extracted from these studies to model PPS on second line lorlatinib, and 2nd line chemotherapy. In this analysis, first-line lorlatinib followed by chemotherapy maintained an overall survival benefit versus alectinib and brigatinib.

2.5.1 The EAG's response

The EAG maintains that key transitions in a four-state model cannot be appropriately represented in a way that fully captures the impact of CNS metastases on QALY gain given currently available data. That is, within the current structure, it is not possible to meaningfully represent the prognosis of a patient with CNS metastases. Specifically, the effects of delaying CNS progression are not appropriately represented by applying post-progression survival outcomes from the wider population of patients with progressed disease. As there is no data to model a structural link between non-CNS PD and CNS-PD, the model cannot fully represent the four-state paradigm of the condition and the impact of secondary CNS progression events on HRQoL.

Even if we disregard these structural issues concerning the four-state approach and consider the most appropriate means to model CNS outcomes given currently available data, it is important to note that the company does not use relevant data from the comparator trials to model CNS outcomes. The company's four-state model assumes that the comparatively large intracranial effect size of lorlatinib compared to crizotinib is unique to lorlatinib. This ignores signals in the ALEX trial suggestive of a similarly increased effectiveness of alectinib compared to crizotinib – which has been shown to have poor intracranial activity compared to alectinib and brigatinib (See Table 3).

The model also does not differentiate between patients with and without CNS metastases at baseline, who are subject to very different risks of non-CNS progression, CNS progression and death. The application of a constant risk of a CNS progression event on the basis of an event rate from one subgroup may lead to clinically implausible proportions of patients experiencing CNS progression when extrapolated out over the modelled period.

Briefly, the approach taken by the company to model the rate of intracranial progression events experienced by alectinib and brigatinib patients is as follows:

- Survival curves were fit to IC-TTP on crizotinib in CROWN.
- The PFS hazard ratios for alectinib and brigatinib vs crizotinib were applied to the crizotinib IC-TTP curve to estimate the CNS-PFS curves for the two comparators.

The curves used by the company to model CNS-PFS are reproduced in Figure 1

Figure 1 Modelled CNS-PFS curves

Assumption of equivalent relative effects across PFS and CNS-PFS

Taking alectinib as an example, the company assume that the CNS-PFS treatment effect is equal to the PFS treatment effect versus crizotinib. This assumption is not supported by the available data from either CROWN or ALEX. The CNS-PFS HR for lorlatinib vs crizotinib is [redacted] compared to a PFS HR of [redacted] (demonstrating lorlatinib has a larger effect on CNS-progression than overall progression). Similarly, for alectinib vs crizotinib, CNS-PFS HRs are 0.18 (patients with baseline CNS mets) and 0.14 (patients without baseline CNS mets) compared to HR of 0.40 and 0.51 for PFS. Therefore, it seems unlikely that the PFS efficacy of a given drug should be equal to its CNS-PFS efficacy. An approach adopting this assumption may therefore underestimate the benefit of alectinib in terms of delaying CNS progression.

In the company submission, it was reasoned that a formal synthesis of CNS-PFS outcomes was not possible because the CROWN study recorded time to intracranial progression (which does not class deaths as events), while the ALEX and ALTA-1L trials recorded intracranial progression free survival – which categorises death as an event. While this difference may preclude formal synthesis of time to event data, the EAG notes that hazard ratios for primary CNS progression events are reported independently of CNS-PFS for alectinib versus crizotinib in the ALEX study.[1] Table 2 presents the comparisons of CNS progression for lorlatinib and alectinib, each with crizotinib. The EAG did not identify equivalent data for brigatinib.

Table 2 Comparison of CNS TTP trial outcomes on lorlatinib and alectinib

Treatment	n	CNS progression without prior non-CNS PD, n (%)

Patients with baseline CNS metastases		
Crizotinib	40	[redacted]
Lorlatinib	38	[redacted]
Hazard ratio (95% CI)		[redacted]
Crizotinib	58	33 (56.9)
Alectinib	64	12 (18.8)
Hazard ratio (95% CI)		**0.18 (0.09 – 0.36)**
Patients without baseline CNS metastases		
Crizotinib	107	[redacted]
Lorlatinib	111	[redacted]
Hazard ratio (95% CI)		[redacted]
Crizotinib	93	35 (37.6)
Alectinib	88	6 (6.8)
Hazard ratio (95% CI)		**0.14 (0.06 – 0.33)**
Treatment		**Weighted average**
Lorlatinib		[redacted]
Alectinib		0.148

While lorlatinib maintains a numerical advantage in HR over alectinib, the confidence intervals are wide and overlapping, with a difference between point estimates very different from the magnitude modelled under the assumption that the CNS-PFS effect size for alectinib vs crizotinib would be equivalent to the PFS effect size.

Whilst the EAG disagrees in principle with the use of a four-state model structure given current data limitations, the use of directly relevant CNS TTP data from ALEX may provide a more appropriate comparison of the relative effectiveness of alectinib for illustrative purposes. A comparison between lorlatinib and alectinib using a weighted average HR for alectinib (0.148) presented in Section 3 illustrates that the CNS benefits generated by lorlatinib over alectinib may be much smaller than in the original scenario presented by the company, with lorlatinib generating only [redacted] more incremental QALYs versus alectinib than when the CNS-PD health state is removed in its entirety. However, it may be that these small differences would be amplified if the prognosis of patients with CNS metastases was appropriately captured in the model. A similar comparison was not possible for brigatinib.

Extrapolating subgroup-specific risks to the wider population

A key issue with the approach taken by the company relates to functional form of the risks which patients are exposed to in the two key sub-populations – those with CNS metastases at baseline, and those without.

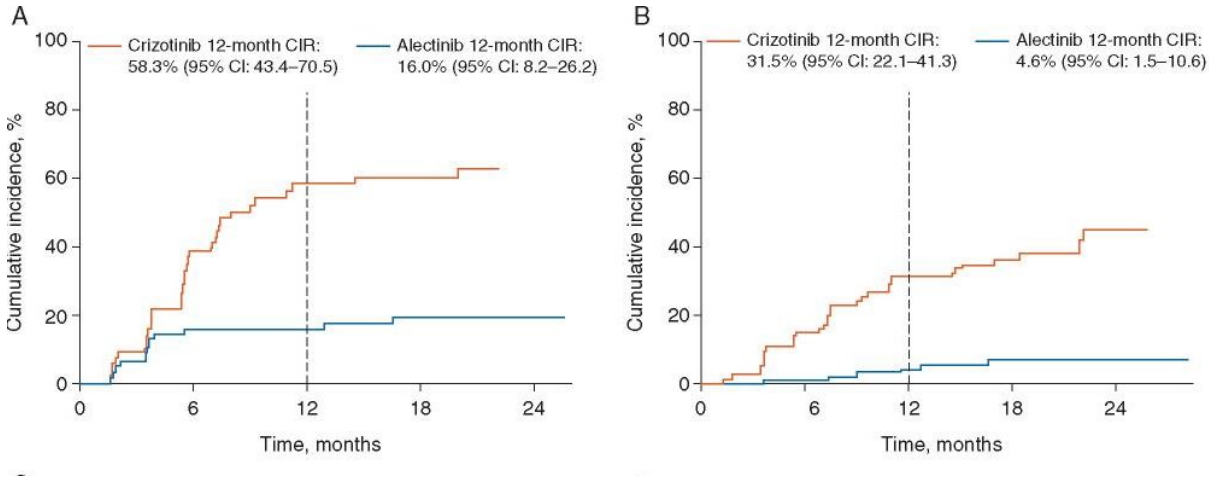
As shown in Table 3, outcomes divided by presence of CNS metastases at baseline show that on lorlatinib, alectinib, and brigatinib, the vast majority of IC progression events occur in those who already had CNS metastases when they began treatment.

Table 3 Observed IC progression by CNS mets at baseline

Treatment (trial)	With brain mets at baseline		Without brain mets at baseline	
	Total	**IC progression observed**	**Total**	**IC progression observed**
Lorlatinib (CROWN) (September 2021)	[redacted]	[redacted]	[redacted]	[redacted]
Crizotinib (CROWN) (September 2021)	[redacted]	[redacted]	[redacted]	[redacted]
Alectinib (ALEX)	**64**	**12 (18.8%)**	**88**	**6 (6.8)**
Crizotinib (ALEX)	58	33 (56.9%)	93	35 (37.6)
Brigatinib (ALTA-1L)	**47**	**21 (45%)**	**90**	**9 (10%)**
Crizotinib (ALTA-1L)	49	29 (59%)	89	16 (18%)

Furthermore, the small number CNS progression events in patients with CNS metastases at baseline on alectinib appear to occur within only a few months of beginning treatment (see plot A, Figure 2), followed by a stable plateau for the remainder of the follow-up period. Conversely, CNS-PFS events on crizotinib in this subgroup appear to occur at a more constant rate for a much longer period. This suggest that CNS progression events in alectinib patients with CNS metastases at baseline are a result of poor initial treatment response, and represent continuing progression of intracranial disease. A visual comparison crizotinib and alectinib appears to show it is unlikely that the assumption of proportional hazards would be met. While the choice of the exponential function is based on the fit to crizotinib data, the assumption that events follow the same pattern on alectinib is inappropriate. The modelling of a constant event rate over the long extrapolation period is not appropriate and does not reflect the apparently rapidly decreasing risks in treated patients over time. This results in clinically implausible predictions of the number of patients with CNS metastases at baseline experiencing CNS PD on alectinib, as events occur at a constant rate over the modelled time horizon.

Figure 2 Cumulative incidence rate of CNS progression in ALEX: A) patients with CNS metastases at baseline, B) patients without CNS metastases at baseline. Gadgeel *et al*.[1]



Risks in the second sub-population (plot B, Figure 2) – those without CNS metastases at baseline, may again follow a different functional form. CNS progression events occur later and represent progression due to loss of disease control.

This heterogeneity in evolution of risks within these two subpopulations cannot be represented using a single parametric function, and within each sub-population this would require the use of a time varying treatment effect which can't be generated using currently available data. In a model better reflecting the prognosis of CNS-PD, different types of risk that each subgroup is subject to will have an impact on the apparent effectiveness of treatment. In an appropriate model structure, this means each subgroup should be modelled separately.

Alternative sources of post-progression survival data

The EAG considered the methods used to identify and implement these alternative sources of PPS data unclear. No formal analysis integrating these data were presented in the DGD response. However, the sources described appeared less relevant than Study 1001 and PROFILE used in the base-case.

2.6 Comment 6: Modelling treatment beyond progression (DGD Section 3.15)

The company accepted the committee's preference for 5.7 months of treatment beyond progression for lorlatinib at first- and second-line. The clinicians present at the first ACM also explained that treatment beyond progression is common for all ALK TKIs in this indication – usually for a period of around three months. The company implemented this in the model in their interpretation of this scenario.

2.6.1 The EAG's response

The original base-case model assumed time on treatment for alectinib and brigatinib was equal to PFS, i.e. it was explicitly assumed that treatment was discontinued at the point of progression. In order to switch to a time-based ToT curve, the model switched to an external data source for its estimate of median time on treatment, and added three months to this, per the clinical advice received by the committee. However, the most recent ToT estimates identified by the company were in excess of BIRC assessed PFS outcomes, for which no later assessments were available. It is also likely that decisions to continue treatment are dependent on investigator assessment of ongoing benefit (rather than objective central assessment of progression).

due to the progression assessment criteria applied in the comparator trials. This means that the model in the company's DGD response assumed that median ToT was 5.8 months longer than median PFS on alectinib, and 3.7 months longer than median PFS on brigatinib. The implementation of the scenario in this way added significant costs to the comparator arms in the company's model.

In the 'corrected' version of the company's revised base case in Section 3, the EAG uses median PFS plus 3 months to calculate median ToT. This results in median ToT of [redacted] months on alectinib and [redacted] months on brigatinib.

The EAG agrees that a 3-month extension to ToT on alectinib and brigatinib is in alignment with clinical advice heard at ACM1, but we did not have the opportunity to verify this with our own clinical expert. The EAG also agrees it is appropriate to assume the additional 5.7 months of treatment applies for second-line lorlatinib, but notes that this effectively doubles the observed duration of treatment in the second-line trial. Given the short duration of PPS in patients eligible for chemo after progression on a first TKI (i.e. mean 9.51 months at 2L in the model), it may be unlikely that treatment continues for this long on average after progression on a second TKI.

While this assumption aligns with the committee's preferences in the DGD, it may inflate total costs in the comparator arms if not representative. Both aspects of treating beyond progression are included in the EAG's revised base-case analysis presented in Section 3.

2.7 Comment 7: Dosing (DGD Section 3.18)

The company argue that the most appropriate method calculating cost-savings associated with dose reductions uses the accurate dosing information from the CROWN study. The company reiterate their concern that the relative dose intensity method is simplified and less accurate.

2.7.1 The EAG's response

The EAG recognises the superiority of using detailed dosing information from CROWN as a means of representing the cost savings associated with dose reductions and missed doses in the trial. The use of this method results in a lower average cost of treatment versus using RDI to model cost savings.

However, the EAG maintains its preference for a consistent approach across lorlatinib and the comparators in the model. There is no evidence to suggest that given the use of equivalent detailed dosing information from the alectinib and brigatinib trials, a commensurate reduction in total costs would not be observed for these treatments. Whilst the real-world costs of lorlatinib may not be accurately captured using RDI, the real-world differences in total costs between lorlatinib, alectinib, and brigatinib may be better reflected when using this approach.

2.8 Additional issues

The company implemented an incomplete interpretation of the committee's preferred assumptions regarding adverse event disutilities. In the DGD, the committee express a preference for the corrected adverse event disutilities and the application of mean AE durations from the CROWN study. In the model submitted in response to the DGD, the company applied only the AE durations from CROWN, and not the full disutilities from the papers referenced.

2.8.1 The EAG's response

The EAG agrees that the most appropriate source for duration data on AEs of special interest is CROWN. However, the disutilities applied in this scenario as presented in the original EAG Report may not be suitable for decision making for a number of reasons. Firstly, the large disutilities reported in the source study may represent an acute case of the events in question, associated with a disutility of up to -0.45. While this may be a reasonable representation of the transient impact of a Grade 4 adverse event such as neutropaenia, it is unlikely that this level of disutility would extend out over the full duration of AEs such as peripheral neuropathy – which were assumed by the company to incur the same level of disutility, but persisted for over a year on average. As these larger disutilities were only sourced by the company for AEs of special interest on lorlatinib, equivalent data on important AEs specific to alectinib and brigatinib were not considered in this scenario. The EAG therefore considers the duration-only approach implemented by the company to be appropriate, and implements this in the updated EAG base case presented in Section 3.

3 COMPANY REVISED BASE CASE AND EAG BASE CASE

As part of the response, the company have provided a revised base-case analysis. The revised base case includes several changes from the base case presented at TE, which are described in Table 4. Bold emphasis signifies where an assumption in the revised company base-case differs from the committee's preferences.

Table 4 Revisions to the company base case

Assumption	Previous base case (at TE)	Committee preferred assumption in DGD	Revised company base-case
Health states	Four state model – CNS PD health state included	Three state model – CNS PD health state removed	**Four state model – CNS PD health state included**
Utilities	CROWN utilities	TA670 utilities	TA670 utilities
Drug acquisition costs	Detailed dosing data from CROWN used to adjust costs	Use RDI for consistency with comparator	**Detailed dosing data from CROWN used to adjust costs**
PFS NMA	ALESIA excluded	ALESIA included	ALESIA included
Treatment effect cap	Not included	10 years	10 years
Treatment beyond progression	Treatment stops at point of progression for all drugs.	Include 5.7 months treatment beyond progression on first- and second- line lorlatinib. Use EAG estimate for proportion of patients progressing to second-line lorlatinib.	Include 5.7 months treatment beyond progression on first- and second- line lorlatinib. Use EAG estimate for proportion of patients progressing to second-line lorlatinib. **Model 3 months treatment beyond progression for first-line alectinib and brigatinib.**
Adverse event disutilities	All AEs assumed to resolve after 5 days.	AE durations based on TA670 (28 days) or CROWN where available. Disutilities aligned with source studies.	**AE durations based on TA670 (28 days) or CROWN where available.**
PFS	Deaths as a proportion of PFS events based on average across CROWN trial arms.	Deaths as a proportion of PFS events based on respective CROWN trial arms.	Deaths as a proportion of PFS events based on respective CROWN trial arms.
PPS	Study 1001 (PPS on 2nd line lorlatinib) and PROFILE (PPS on 2nd line chemotherapy) used to model PPS.	Alternative data sources should be explored.	Alternative data sources explored. Maintains use of Study 1001 and PROFILE to model PPS.

3.1.1 Results of updated company analysis

Table 5 presents the results of the company's revised base case, according to the company's interpretation of the committee's preferred set of assumptions. As noted in Section 2.6, the EAG

identified an error in the implementation of the scenario modelling treatment beyond progression. Table 6 presents the results of the company's revised base case correcting for this error as described in Section 2.6.

These results include only the confidential PAS discount for lorlatinib and are exclusive of confidential commercial arrangements for the comparator treatments. Results with discounts for all comparators and subsequent treatments are provided in a confidential appendix to this addendum.

Table 5 Company's revised base case (pairwise) – Lorlatinib PAS only

Treatment	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Brigatinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

Table 6 EAG-corrected company revised base case (pairwise) – Lorlatinib PAS only

Treatment	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Alectinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Brigatinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

A further scenario described in Section 2.5.1 is presented in Table 7. This scenario presents an illustrative pairwise comparison of alectinib and lorlatinib, in which the naïve time to CNS progression hazard ratio for alectinib vs crizotinib from the ALEX trial is applied to model membership of the CNS-PFS health state on alectinib. This analysis uses the corrected base case in Table 6 as a basis. In this analysis, lorlatinib generates only [redacted] more incremental QALYs versus alectinib than when the CNS-PD health state is removed in its entirety.

Table 7 Scenario modelling CNS-PFS HR from ALEX for alectinib – Lorlatinib PAS only

Treatment	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Alectinib	[redacted]	[redacted]	[redacted]				

Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

3.1.2 EAG updated base case

Table 9 presents an updated EAG base-case analysis, which reflects the committee's preferences from ACM1 and accounts for issues raised in the company's DGD response. The assumptions made in this analysis are in the rightmost column of Table 8.

Table 8 EAG updated base-case assumptions

Assumption	Committee preferred assumption in DGD	Revised company base-case	Revised EAG base-case
Health states	Three state model – CNS PD health state removed	**Four state model – CNS PD health state included**	Three state model – CNS PD health state removed
Utilities	TA670 utilities	TA670 utilities	TA670 utilities
Drug acquisition costs	Use RDI for consistency with comparator	**Detailed dosing data from CROWN used to adjust costs**	Use RDI for consistency with comparator
PFS NMA	ALESIA included	ALESIA included	ALESIA included
Treatment effect cap	10 years	10 years	10 years
Treatment beyond progression	Include 5.7 months treatment beyond progression on first- and second- line lorlatinib. Use EAG estimate for proportion of patients progressing to second-line lorlatinib.	Include 5.7 months treatment beyond progression on first- and second- line lorlatinib. Use EAG estimate for proportion of patients progressing to second-line lorlatinib. **Model 3 months treatment beyond progression for first-line alectinib and brigatinib.**	Include 5.7 months treatment beyond progression on first- and second- line lorlatinib. Use EAG estimate for proportion of patients progressing to second-line lorlatinib. **Model 3 months treatment beyond progression for first-line alectinib and brigatinib. (corrected)**
Adverse event disutilities	AE durations based on TA670 (28 days) or CROWN where available. Disutilities aligned with source studies.	**AE durations based on TA670 (28 days) or CROWN where available.**	**AE durations based on TA670 (28 days) or CROWN where available.**
PFS	Deaths as a proportion of PFS events based on respective CROWN trial arms.	Deaths as a proportion of PFS events based on respective CROWN trial arms.	Deaths as a proportion of PFS events based on respective CROWN trial arms.
PPS	Alternative data sources should be explored.	Alternative data sources explored. Maintains use of Study 1001 and PROFILE to model PPS.	Study 1001 and PROFILE used to model PPS.

Table 9 EAG updated base case following DGD (pairwise) – Lorlatinib PAS only

Treatment	Total costs	Total LYs	Total QALYs	Inc. costs	Inc. LYs	Inc. QALYs	ICER
Alectinib	[redacted]	[redacted]	[redacted]				

Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant
Brigatinib	[redacted]	[redacted]	[redacted]				
Lorlatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Dominant

4 REFERENCES

1. Gadgee S, Peters S, Mok T, Shaw AT, Kim DW, Ou SI et al. "Alectinib versus crizotinib in treatment-naive anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study." *Annals of Oncology* 2018; **29**: 2214-2222.