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

Part 1 Slides for public - All confidential information redacted

Technology appraisal committee D [19 January 2023]

Chair: Megan John

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Company: Pfizer

Updated approach to health technology evaluations: new methods and processes

This topic uses NICE's updated methods for health technology evaluations, 2022: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

Updates fall under 5 headings:

- Valuing the benefits of health technologies
- Understanding & improving the evidence base
- Structured decision making
- Challenging circumstances and evaluations
- Aligning methods across programmes

Including:

- Severe and end-of-life conditions ("modifiers")
- Presenting and considering uncertainty
- Technical updates – including comprehensive evidence base
- Consolidation and alignment for different technology types (medicines, devices, diagnostics)

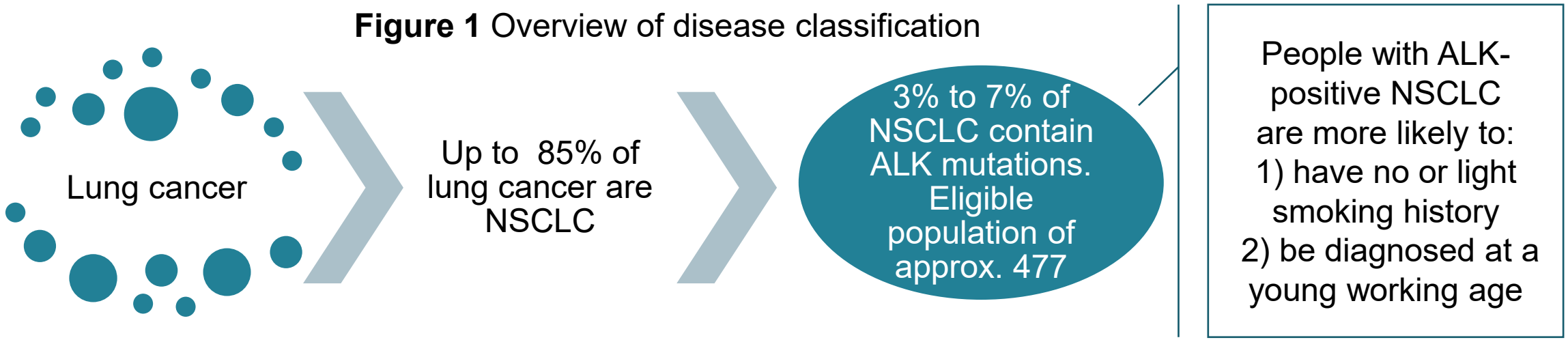
Disease background

People with ALK- positive advanced NSCLC often have advanced disease at time of diagnosis

Epidemiology, classification, causes

- Lung cancer is the third most common cancer
- In 2018 approximately 39,754 people were diagnosed with NSCLC in England & Wales, of whom 49% had stage IV disease

Figure 1 Overview of disease classification



Symptoms and prognosis

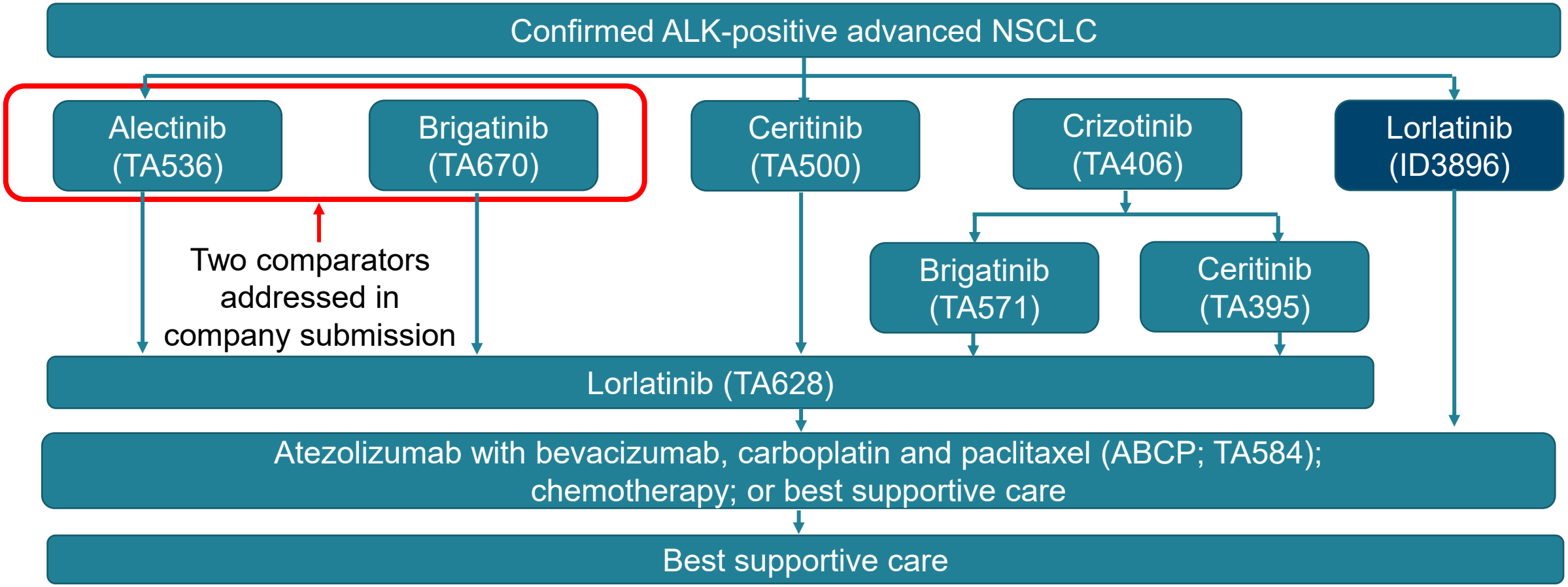
- People often have advanced disease at time of diagnosis
- Leads to poor HRQoL (for example, pain, breathlessness, persistent cough)
- Brain metastases highly prevalent (up to 30% have brain metastases at diagnosis)
- Brain metastases associated with significant morbidity (for example, drowsiness, severe headaches, confusion)

Abbreviations: ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; HRQoL, health-related quality of life

Treatment pathway

Company propose lorlatinib in the first-line setting

Figure 2 Company's proposed treatment pathway for people with ALK-positive advanced NSCLC in UK clinical practice



What are the most appropriate comparators for the lorlatinib?

Abbreviations: ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TA, technology appraisal

Patient perspectives

Patients report fewer side effects with lorlatinib versus other TKIs. They are manageable

Submissions from a patient expert, ALK Positive UK and Roy Castle Lung Foundation

- Lorlatinib is very well tolerated in the 2nd line setting and we believe this would be no different in the 1st line setting
- Approval of 1st line use would give oncologists more choice to choose the most appropriate treatment for each patient
- Important to have treatment options which demonstrate both overall and intracranial effectiveness
- Effective management of brain metastases is vital for a good QoL for people and the chance to be stable for as long as possible
- Patients report that lorlatinib has fewer side effects than current TKIs, people don't report sun-burning which occurs with alectinib
- Need for additional more effective treatments in this patient group

'These people are young, with families, many still contributing to the economy and society'

'These people are never smokers- many were very fit and healthy'

NICE

Abbreviations: ALK, Anaplastic lymphoma kinase; QoL, quality of life; TKIs, tyrosine kinase inhibitors

Clinical perspectives

Clinicians have experience of lorlatinib and managing the adverse events as it is already used in the second-line setting

Submissions from clinical experts, Newcastle upon Tyne Hospitals NHS Trust and British Thoracic Oncology Group

- There continues to be unmet need in patients with ALK lung cancer, lorlatinib would be a useful addition to the first line treatment options
- Control of CNS disease remains a key outcome for clinicians and patients
- A response rate of greater than 60% and a PFS of greater than 2 years would be considered a clinically significant treatment response
- There are significant side effects associated with lorlatinib with those observed in clinical practice similar to those seen in clinical trials
- Some of the AEs seen with lorlatinib have minimal clinical impact such as elevated cholesterol combat but others can have a major impact on QoL including neuropathy and mood disturbance
- Lorlatinib may be slightly more toxic than alectinib and brigatinib and may require closer monitoring or clinician input into toxicity management

‘There are significant side effects associated with lorlatinib with those observed in clinical practice similar to those seen in clinical trials’

‘….most clinicians have experience of the drug and managing adverse events’

Abbreviations: ALK, Anaplastic lymphoma kinase; CNS, central nervous system; QoL, quality of life; AEs, adverse events; PFS, progression-free survival

Other considerations

Equality considerations (company)

- No equalities considerations identified

Equality considerations (patient organisation)

- A need for a guideline as patients being treated at small district general hospitals, where the oncologists may not specialise in lung cancer, or have experience with ALK NSCLC, are very likely to be disadvantaged (ALK Positive UK)

Innovation (company)

Lorlatinib's design allows high blood-brain barrier penetration, leading to high exposures in the CNS and marked IC activity

- Lorlatinib has been recognised as innovative at the regulatory level in the UK, where the MHRA granted lorlatinib an Innovation Passport on 1st March, 2020

Are all relevant benefits associated with innovation captured in the model?

Abbreviations: ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; MHRA, Medicines and Healthcare products Regulatory Agency; IC, Intracranial; CNS, central nervous system

Key issues (1)

Clinical effectiveness evidence

Table 1 Key issues

Issue	Resolved?	ICER impact
Obsolete ALK inhibitor treatment sequences used in the CROWN trial	No – for discussion	Unknown 
Very few participants with an ECOG performance status score of 2 were recruited into the CROWN trial	No* – for discussion	Unknown 
Immature overall survival data from the CROWN trial	No* – for discussion	Unknown 
Baseline CNS metastases as a potential treatment effect modifier	No* – for discussion	Unknown 
Exclusion of the ALESIA study from the NMA used in the economic model	No* – for discussion	Small 
Incidence of grade ≥ 3 adverse events with lorlatinib compared to other ALK inhibitors	Partially – for discussion	Small 

* May be partly resolved by data collection in CDF

Abbreviations: ALK, Anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group Performance Status; PFS, progression-free survival; OS, overall survival; CNS, central nervous system; NMA, network meta-analysis

Key issues (2)

Cost effectiveness evidence

Table 1 continued Key issues

Issue	Resolved?	ICER impact
Insufficient data available to model CNS PD health state appropriately	No – for discussion	Large
PFS benefit is uncertain due to immaturity of data from CROWN:	Partially – for discussion	Unknown
HRQoL data from CROWN not reflective of real-world utilities	Partially – for discussion	Large
Treatment beyond progression on lorlatinib is likely	Partially – for discussion	Small
Dosing calculations	Partially – for discussion	Large
Resolved issue (not discussed)	**Resolved?**	**ICER impact**
Death not modelled as a PFS event	Yes	N/A

Abbreviations: PFS, progression-free survival; CNS, central nervous system; PD, progressive disease; HRQoL, Health-related quality of life

Lorlatinib (Lorviqua, Pfizer)

Table 2 Technology details

Marketing authorisation	• Lorlatinib as monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor or whose disease has progressed after prior treatment with an ALK inhibitor • MHRA marketing authorisation granted 23rd September 2021
Mechanism of action	• Lorlatinib inhibits the ALK and ROS1 receptor tyrosine kinases, acting against a range of ALK resistant mutations • By inhibiting ALK phosphorylation and ROS1 activity, lorlatinib inhibits the downstream signalling, inducing cell death, which results in the inhibition of tumour cell growth
Administration	• The recommended dose is 100 mg taken orally once daily
Price	• List price for lorlatinib of £5,283.00 per 30 x 100 mg 90 x 25 mg tablets • A patient access scheme is available for lorlatinib

Abbreviations: ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; MHRA, Medicines and Health Regulatory Agency; ROS proto-oncogene 1

Decision problem

Comparator from CROWN (crizotinib) not used in NHS so NMA conducted

Table 3 Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	Adults with untreated ALK-positive advanced NSCLC	Adults with ALK-positive advanced NSCLC that has not been previously treated with an ALK inhibitor (aligned with MA)	EAG's clinical adviser considered company's proposed population to be appropriate
Intervention	Lorlatinib	Same as final scope	MA recommends once-daily 100mg dose which reflects how lorlatinib was studied in CROWN
Comparators	• Alectinib • Brigatinib • Ceritinib • Crizotinib	• Alectinib • Brigatinib	EAG's clinical adviser agreed alectinib and brigatinib represent current clinical practice and ceritinib and crizotinib rarely used
Outcomes	OS, PFS, Response rates, Adverse effects of treatment, HRQoL	OS, PFS, Response rates, Intracranial outcomes, Adverse effects of treatment, HRQoL	OS data were particularly immature though CROWN's statistical analysis plan did not permit another interim data cut

Abbreviations: ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; HRQoL, health-related quality of life; MA, marketing authorisation; NMA, network meta-analysis; PFS, progression-free survival; OS, overall survival

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key clinical trial

Overall survival data from CROWN trial are immature

Table 4 Clinical trial designs and outcomes

	CROWN (NCT03052608)
Design	Phase 3, multicentre, open label, parallel, two-arm randomised trial
Population	Adults with advanced ALK-positive NSCLC who had received no previous systemic treatment for metastatic disease
Intervention	Lorlatinib 100 mg, oral once daily
Comparator(s)	Crizotinib 250 mg, oral twice daily
Median duration of follow-up*	Lorlatinib PFS: [redacted]; crizotinib PFS: [redacted] Lorlatinib OS: [redacted]; crizotinib OS; [redacted]
Primary outcome	PFS based on BICR assessment
Key secondary outcomes	OS, PFS based on investigator's assessment, response rates, IC outcomes, adverse effects of treatment, HRQoL
Locations	Multinational (104 sites in 23 countries [3 UK sites])
Used in model?	Yes

OS data immature and was not measured at September 2021 DCO but the March 2020 DCO

Further data-cuts for OS of the CROWN trial are scheduled for [redacted] and [redacted]

*PFS measured at September 2021 DCO; OS measured at March 2020 DCO

Abbreviations: ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; PFS, progression-free survival; BICR, blinded independent central review; OS, overall survival; IC, intracranial outcomes; HRQoL, health-related quality of life; DCO, data cut-off

CROWN trial baseline characteristics

Table 5 Baseline characteristics for intervention and comparator

Characteristic	Lorlatinib (n=149)	Crizotinib (n=147)
Age Mean, years (SD)	59.1 (13.1)	55.6 (13.5)
Sex		
Female, n (%)	84 (56)	91 (62)
Male, n (%)	65 (44)	56 (38)
Race or ethnic group		
White, n (%)	72 (48)	72 (49)
Asian, n (%)	65 (44)	65 (44)
Black, n (%)	0	1 (1)
Missing, n (%)	12 (8)	9 (6)
ECOG PS score		
0, n (%)	67 (45)	57 (39)
1, n (%)	79 (53)	81 (55)
2, n (%)	3 (2)	9 (6)
Brain metastases at baseline n (%)	38 (26)	40 (27)

EAG Comments

- More than 95% had ECOG PS scores of 0 or 1
- Little data on efficacy of lorlatinib in patients with an ECOG PS of 2
- EAG's clinical adviser considered that proportion of patients with an Asian background is higher than would be seen in NHS

Are these baseline characteristics generalisable to NHS clinical practice?

Abbreviations: SD, standard deviation, ECOG PS: Eastern Cooperative Oncology Group Performance Status

CROWN results: progression free survival

Lorlatinib versus crizotinib showed a clinically meaningful improvement in BICR-assessed PFS

Figure 3 Kaplan–Meier plot of PFS based on BICR assessment (RECIST v1.1), FAS (September 2021 DCO)

Comparison versus crizotinib (stratified analysis):

- HR of [redacted] (95% CI: [redacted], [redacted]; stratified 1-sided p-value [redacted])

Endpoint	Lorlatinib (N=149)	Crizotinib (N=147)
Median (95% CI) PFS, months	[redacted]	[redacted]
Median duration of follow-up	[redacted]	[redacted]

Abbreviations: DCO, data cut-off; BICR, blinded independent central review; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumour version 1.1

CROWN results: overall survival

Robust conclusions cannot be drawn from the overall survival data yet

Figure 4 Kaplan–Meier plot of OS; FAS (March 2020 DCO)

- Overall survival data are still immature from CROWN, and were not measured at September 2021 DCO
- Company presents OS data from March 2020 DCO

Comparison versus crizotinib (stratified analysis):

- HR of 0.72 (95% CI: 0.41, 1.25)

Endpoint	Lorlatinib (N=149)	Crizotinib (N=147)
Median (95% CI) PFS, months	[redacted]	[redacted]
Median duration of follow-up	[redacted]	[redacted]

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Abbreviations: DCO, data cut-off; CI, confidence interval; FAS, full analysis set; HR, hazard ratio; OS, overall survival

Key issue: Obsolete ALK inhibitor treatment sequences used in CROWN trial

Treatment sequences in CROWN trial have limited applicability to NHS practice

Background

- Treatment: 2nd line use of alectinib after lorlatinib not aligned with NHS practice
- Comparator: 1st line crizotinib and 2nd line alectinib, brigatinib, or another ALK inhibitor not aligned with NHS
- EAG concerned that treatment sequences seriously limit applicability of CROWN results to NHS setting

Company

- Crizotinib was the relevant comparator at time of CROWN design
- Acknowledged use of crizotinib in CROWN has limited use in NHS practice
- In absence of trials directly comparing lorlatinib to alectinib and brigatinib, NMAs were conducted to evaluate the comparative efficacy of lorlatinib vs comparators

Clinical expert

- Trial approach wouldn't be used in UK; subsequent treatments based on chemotherapy ± immunotherapy

EAG comments

- Alectinib & brigatinib were used as subsequent treatments in CROWN and second-line use of alectinib after lorlatinib falls outside of alectinib's MA
- Issue of unrepresentative comparators & treatment sequences in evidence-base can only be resolved by a future trial

How much bias do the treatment sequences in CROWN introduce?

Abbreviations: ALK, Anaplastic lymphoma kinase; DCO, data cut-off; NSCLC, non-small cell lung cancer; MA, marketing authorisation

Key issue: Very few participants with an ECOG performance status score of 2 were recruited into the CROWN trial

Lack of trial efficacy data of lorlatinib in patients with ECOG PS scores ≥2

Background

- People with ECOG PS score of 2 eligible for inclusion in CROWN, but 96% of recruited had score of 0 or 1
- ECOG PS of 0 or 1 similar for comparator trials: ALTA 1 (96%) and ALEX (93%)
- ECOG PS score thought to be a prognostic indicator of PFS and OS

Company

- Presented data from National Lung Cancer Audit (2022) suggesting a significant proportion of patients may present with an ECOG PS ≥2 (40% in 2020) [note that this value is not specific to ALK-positive population]
- Clinical feedback advised 25-30% of patients have PS ≥2, but true PS often difficult to measure in ALK-positive patients who tend to be younger and without co-morbidities

Clinical expert

- Majority of ECOG PS 2 patients will respond quickly to treatment resulting in ECOG PS improving to 0 /1

EAG comments

- Lack of trial efficacy data for patients with ECOG PS ≥2 and plausible lorlatinib is less effective in subgroup
- Data collection in CDF may help confirm if patients with an ECOG PS ≥2 are given lorlatinib in NHS practice

Can the results of CROWN be generalised to people with an ECOG PS of 2?

NICE

Abbreviations: ALK, Anaplastic lymphoma kinase; ECOG, Eastern Cooperative Oncology Group Performance Status; PFS, progression-free survival; OS, overall survival; MA, marketing authorisation; CDF, cancer drugs fund

Key issue: Immature overall survival data from CROWN trial

Uncertainty in overall survival estimates remains

Background

- OS data from CROWN were not measured at the September 2021 DCO
- Company noted that OS data from CROWN are still immature and no robust conclusions can be drawn
- Company use OS data from March 2020 DCO (no significant difference between groups found for OS)
- EAG noted there is currently no evidence that increased PFS from lorlatinib leads to increased OS

Company

- Acknowledge there remains substantial uncertainty in OS estimates for lorlatinib and the relationship between PFS and OS
- Cannot provide any additional evidence at this time to address this uncertainty
- Data maturity will help address this issue, with the next data cuts planned for [redacted]

EAG comments

- Agree with the company's view, though notes that longer-term data will be limited because patients in CROWN received treatment sequences which are not used in the NHS (e.g. second-line alectinib after first-line lorlatinib)

Would more mature data from CROWN help to resolve the uncertainty?

Abbreviations: PFS, progression-free survival; OS, overall survival; DCO, data cut-off

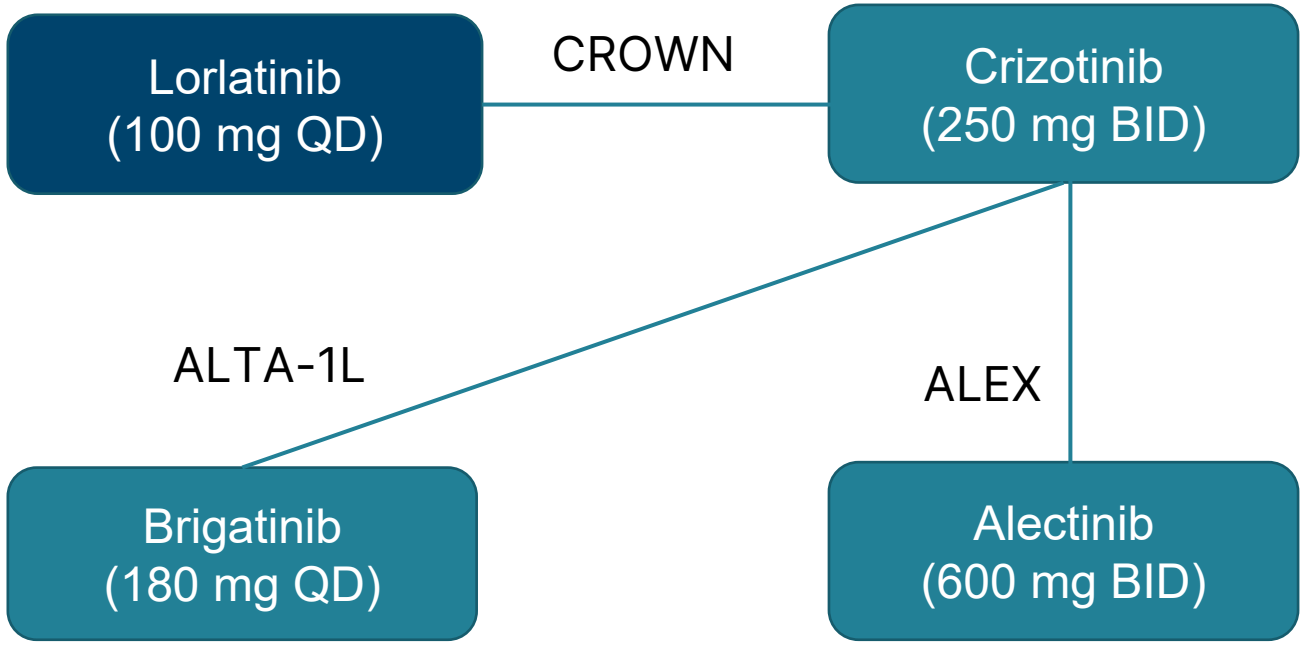
NMA network diagram

- No head-to-head studies identified directly comparing lorlatinib to alectinib and brigatinib, therefore Bayesian NMAs conducted to assess relative efficacy and safety of lorlatinib vs comparators

Approach

- A standard Bayesian NMA was conducted
- A fixed effects model was used in both analyses of PFS and OS

Figure 5 PFS and OS resulting network diagram, following the exclusion of ALESIA



EAG Comments

- Company didn't provide full data, inputs and source code used to run all NMAs as requested. Difficult for EAG to identify source of NMA inputs, and validate results
- Company didn't provide an indirect comparison on incidence of grade 3-4 adverse events as requested
- No baseline adjustments were conducted for baseline differences

Abbreviations: NMA, network meta-analysis; RCTs, randomised-controlled trial; MCMC, Markov Chain Monte Carlo

NMA results

No robust conclusions can be made from the OS data due to the immaturity of OS data from CROWN

Table 6 PFS/OS relative effect of lorlatinib compared with all treatments (fixed effects)

	Treatment	HR (95% CrI)
PFS September 2021 DCO	Alectinib (600 mg BID)	[redacted]
	Brigatinib	[redacted]
OS March 2020 DCO	Alectinib (600 mg BID)	[redacted]
	Brigatinib	[redacted]
Data on serious adverse events not provided		

Progression-free survival

- Lorlatinib showed a [redacted] improvement in PFS for both comparisons (September 2021 DCO)

Overall survival

- OS showed [redacted] between lorlatinib and both comparisons (March 2020 DCO)
- OS data from CROWN still very immature, therefore no conclusions could be drawn from this analysis

Abbreviations: BID, twice daily; CrI, credible interval; HR, hazard ratio; NR, not reported; PFS, progression-free survival

Key issue: Baseline CNS metastases as a potential treatment effect modifier

EAG uncertain whether presence of CNS metastases affects PFS across ALK-TKIs

Background

- Alectinib and brigatinib trials in NMA recruited more patients with CNS metastases at baseline than CROWN (lorlatinib 26%, crizotinib 27%), ALEX (alectinib 42%, crizotinib 38%); ALTA-1L (brigatinib 29%, crizotinib 30%)
- EAG concerned discrepancies in proportion of patients with CNS metastases at baseline may be indicative of a different average prognosis and potential treatment effect between populations
- Published NMAs show (1) versus alectinib: no evidence that baseline CNS metastases impact PFS, but (2) versus brigatinib: potential impact where lorlatinib was more effective in people without CNS metastases
- No cost-effectiveness results by subgroup provided

Company

- Summarised uncertainty surrounding PFS results for this subgroup, but did not present new data
- Clinical experts advised approximately one third of patients present with baseline brain metastases
- Data collection in CDF will validate generalisability of baseline characteristics in CROWN to clinical practice

EAG comments

- Unclear how additional data collection in CDF could help to resolve this issue, given uncertainty on if the presence of CNS metastases affects PFS across the different ALK-TKIs
- Longer follow-up data from CROWN may help reduce uncertainty

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What additional data would help to resolve this issue?

Abbreviations: AEs, adverse events; CNS, central nervous system; NMA, network meta-analysis

Key issue: Exclusion of ALESIA study from NMA used in model

EAG disagrees with the exclusion of ALESIA from network meta-analysis

Background

- 4 RCTs identified (including CROWN) and considered for inclusion in NMA
- Company excluded ALESIA study of alectinib (Asian patients only) from NMA noting it was not considered representative of UK population
- EAG note many sites in CROWN were in Asia which may impact OS, but these are not used in model, but shouldn't impact PFS
- EAG commented that inclusion of ALESIA makes alectinib evidence base more comparable to lorlatinib, and reduces apparent efficacy of lorlatinib relative to alectinib, and its cost-effectiveness
- EAG's prefer to use the 'Global NMA' results, which includes ALESIA

Company

- Acknowledge EAG's concerns around the exclusion of ALESIA in NMA
- Presented a scenario analysis for the inclusion of ALESIA in clarification question response
- Noted that in TA670 ALESIA was excluded from the ITC as only east Asian patients were enrolled in the trial

EAG comments

- EAG noted that the company presented no new information on this issue at TE
- Maintains preferred approach to use the 'Global NMA' results (though notes small difference in the ICER)

Should the global NMA results be used in the model?

Abbreviations: NMA, network meta-analysis; TA, technology appraisal ITC, indirect treatment comparison; TE, technical engagement

Partially resolved: Incidence of grade ≥ 3 adverse events with lorlatinib compared with other ALK inhibitors

Background

- Grade 3 or 4 AEs occurred in ([redacted]) of patients receiving lorlatinib and ([redacted]) receiving [redacted] in CROWN
- Company didn't provide an indirect treatment comparison on incidence of grade 3-4 AEs (requested by EAG)
- EAG identified NMAs reporting lorlatinib was associated with an increased risk of grade ≥ 3 AEs vs alectinib (Ando et al, 2021: RR 1.92, 95% CrI, 1.49 to 2.48; Chuang et al, 2021: RR 1.62, 95% CrI 1.24 to 2.12)

Company

- Agree that the side effect profile is different for lorlatinib vs alectinib/brigatinib
- Treatment discontinuation rates observed in clinical trials also indicate that lorlatinib is tolerable to patients

Clinical expert:

- Similar toxicity profile expected in 1st & 2nd line, but 1st line exposure (hence toxicities) likely more prolonged

EAG comments

- Summarised results from 3 NMAs (Ando et al, Chuang et al, Wang et al [2021]) comparing incidence of grade ≥ 3 AEs across ALK inhibitors
- It's important that that analyses comparing relative safety of ALK inhibitors are presented, given lorlatinib's [redacted] improvement in PFS compared to other ALK inhibitors

How does the incidence of grade ≥ 3 AEs for lorlatinib compare with other ALK inhibitors?

Abbreviations: AEs, adverse events; NMA, network meta-analysis; RR, relative risk; CrI, credible interval

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

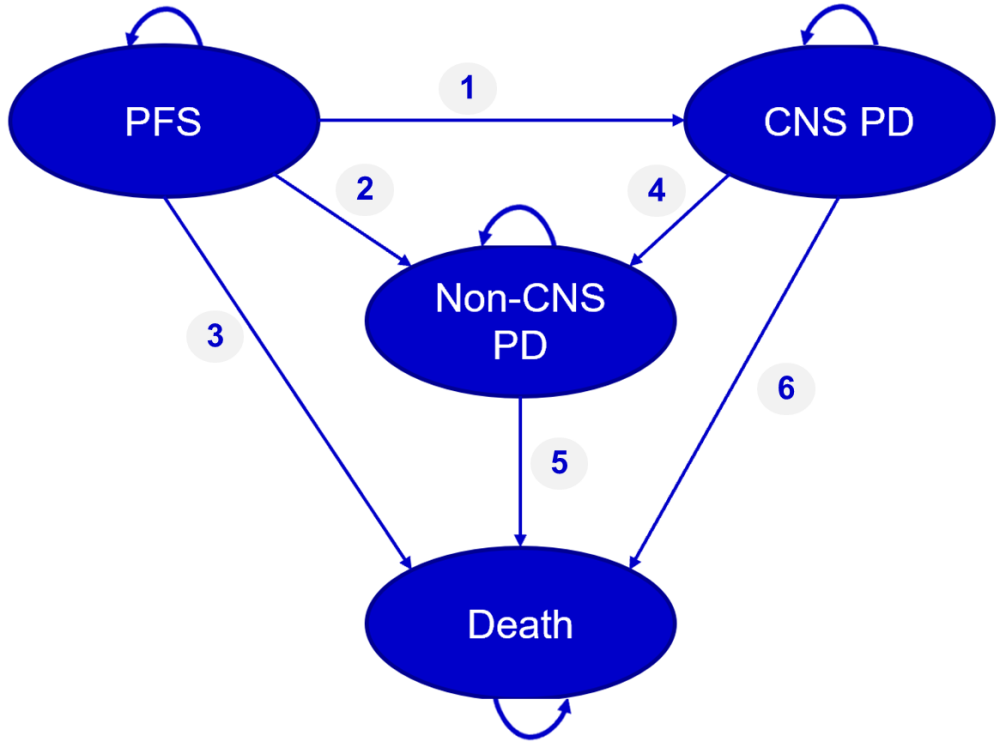
Company's revised model post clarification meeting adopts a pseudo state-transition model

Technology affects **costs** by:
- Increasing first-line treatment costs
- Decreasing subsequent treatment costs

Technology affects **QALYs** by:
- Increasing PFS
- Increasing overall survival
- Reducing the proportion of patients who develop intracranial metastases

Assumptions that drive ICER:
- The size of the PFS benefit for lorlatinib
- The size of the CNS PFS benefit for lorlatinib
- The utility value set selected

Figure 6 Model structure*



EAG Comments
- PFS state could not progress to death (resolved at TE)
- Transition between non-CNS PD and CNS PD not modelled in either direction
- No patients have CNS metastases at model entry
- Inappropriate application of PPS data to CNS-PD state

*The data used against each number is explained on the next slide
PFS, progression-free survival; PPS, post-progression survival; PD, progressive disease; CNS, central nervous system; ICER, incremental cost-effectiveness ratio; TE, technical engagement; QALY, quality-adjusted life year

How company incorporated evidence into model

CROWN data contributed most evidence used in the model

Table 7 Input and evidence sources in the company base case model

Input	Assumption and evidence source
Efficacy (numbers refer to previous slide)	1. CNS-PFS; (CROWN & HR from NMA) 2. PFS- CNS-PFS; (CROWN & HR from NMA) 3. Proportion of PFS events that are deaths (assumption) 4. PFS -CNS-PFS; (CROWN & HR from NMA) 5 & 6. Constant PPS transition rate calculated from second-line OS (Study 1001 (lorlatinib) & PROFILE 1001/1005 (chemotherapy))
Baseline characteristics	CROWN population characteristics
Utilities	CROWN (EQ-5D-5L mapped to EQ-5D-3L using Hernández-Alava algorithm)
Costs and resource use	NHS reference costs, PSSRU Unit Costs of Health and Social Care, previous NICE appraisals (validated by clinical experts), MIMS and eMIT

Abbreviations: PFS, progression-free survival; PPS, post-progression survival; CNS, central nervous system; NMA, network meta-analysis; EQ-5D-XL, EuroQol 5 dimensions X levels; eMIT, Electronic marketing information tool; PSSRU, Personal Social Services Research Unit; Monthly Index of Medical Specialities

Key issue: Insufficient data available to model CNS-PD health state appropriately (1)

EAG prefer to remove CNS-PD health state from the model

Background

- EAG agree with company that 4 state model is conceptually better
- EAG concerned about parameterisation and modelling of CNS-PD in company's updated model
- EAG note that its inclusion is inappropriate and potentially misleading (immature data means uncertainty associated with very optimistic CNS-PFS outcomes cannot be evaluated; intracranial outcomes not comparable between trials; link between non-CNS PD and CNS-PD not modelled; differential prognosis of patients with intracranial metastases at entry into model are not reflected in post-progression survival
- EAG suggested CNS-PD health state removed from model

Company

- Acknowledged that there were no data from CROWN to inform transitions between non-CNS and CNS-PD health states due to censoring
- Division of progressed health state into non-CNS PD and CNS-PD relevant as CNS progression can have a substantial impact on a patient's QoL
- Four-state model previously accepted in TA536 and TA670
- Impact on the ICER can be explored through a scenario analysis varying a per cycle transition rate between non-CNS-PD & CNS-PD health states of 10% - 90% per cycle (scenario results presented in part 2)

Abbreviations: CNS-PD, central nervous system progressed-disease; ICER, incremental cost-effectiveness ratio; QoL, quality of life; TA, technology appraisal

Key issue: Insufficient data available to model CNS-PD health state appropriately (2)

EAG comments

- Recognises precedent of a 4 state model in TA536 and TA670, but notes those circumstances differed from current appraisal: evidence availability and the decision context
- Notes company's base-case assumed significant benefits versus alectinib and brigatinib, with little statistical support and poor comparability of outcome assessment
- Unclear how rates in company's scenarios were implemented
- No new data (post clarification meeting) were provided to inform the transitions
- Benefits modelled are not reflective of clinical experience and outcomes, and attempt to translate a qualitative prediction into a quantitative analysis
- Note structural link between non-CNS-PD and CNS-PD appeared incorrectly implemented by company: scenarios did not pass simple validation tests (increasing per cycle rate of CNS progression events only affects progression rate between the PFS and non-CNS-PD health states)
- Maintains that the three-state model is most appropriate

Is a 4 state model relevant?
Is there sufficient evidence to support this approach for lorlatinib?

Abbreviations: CNS-PD, central nervous system progressed-disease; PFS, progression-free survival

Partially resolved: PFS benefit is uncertain due to immaturity of data from CROWN (1)

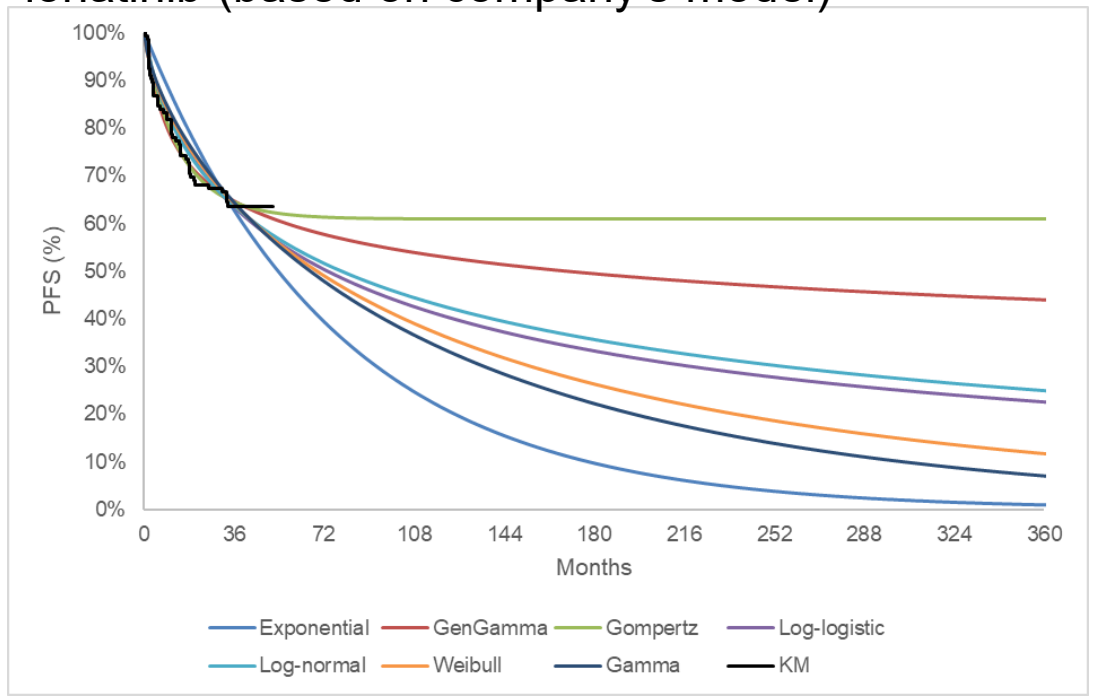
Background

- EAG notes that company choice of exponential to extrapolate PFS in the model for lorlatinib has a poor visual fit to observed data, overestimates PFS compared to the KM data and likely generates optimistic long-term outcomes. However alternatives are less credible.
- EAG requested alternative survival analysis techniques to explore effect of using other extrapolations of PFS

Table 8 Proportion of patients alive and progression free at key time points – lorlatinib

Distribution	Modelled landmarks (years)					
	1	5	10	15	20	30
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Figure 7 Comparison of PFS extrapolations – lorlatinib (based on company's model)



Abbreviations: PSM, partitioned survival model; PFS, progression-free survival

Partially resolved: PFS benefit is uncertain due to immaturity of data from CROWN (2)

Company presented two-piece and cubic spline models to PFS data from CROWN

Company

- Presented flexible parametric survival models to BICR PFS data from CROWN (two-piece and cubic spline)
- Curves showed improved visual and statistical fit to both treatment arms (for two-piece models)
- Statistical fits for spline models remain similar and were better than exponential model in original submission
- Noted survival estimates produced by spline models too optimistic to be clinically plausible

EAG comments

- Agrees better fit of two-piece and spline models may not mean they present clinically plausible alternatives
- Satisfied company explored full range of realistic approaches to survival analysis using the data available
- Issue resolved in context of current data limitations, but notes future data cuts will reduce uncertainty

Is the use of the exponential curve appropriate for decision making?

Abbreviations: PSM, partitioned survival model; BICR, blinded independent central review; PFS, progression-free survival

Partially resolved: HRQoL data from CROWN not reflective of real-world utilities

EAG prefers to use utility set from TA670

Background

- EAG note PD utility is much higher than in previous appraisals
- EAG note division of utilities by treatment status meant patients experiencing a TRAE didn't contribute to utility values applied in model, so reported toxicities associated with lorlatinib not reflected in modelled utilities
- EAG's prefer utility set from TA670 (brigatinib) as believe it is more realistic of the impact of PD on HRQoL
- Company did not comment on the EAG's approach to utilities & modelling AE disutilities – unclear on position

Table 9 Comparison of modelled utilities with previous appraisals

Appraisal	Treatment	Progression-free		Progressed		CNS-progressed	
		On	Off	On	Off	On	Off
Current appraisal (lorlatinib 1st line) (company preference)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TA670 (Brigatinib) (EAG preference)	Brigatinib	0.793	0.793	0.624	0.552	-	0.543
	Alectinib	0.793	0.793	0.624	0.550	-	0.539
TA536 (Alectinib)	Alectinib	0.814	0.814	0.725	0.725	0.52	0.52

Is the company approach or EAG approach to incorporation of HRQoL preferred?

Abbreviations: PD; progressed disease; HRQoL, health-related quality of life; TRAE, treatment-related adverse event; TA, technology appraisal

Partially resolved: Dosing calculations

EAG prefer to use RDI to model acquisition costs for all treatments

Background

- Company used detailed dosing data from CROWN to estimate proportion of patients receiving lower dose of lorlatinib. For comparator treatments, RDI was applied in model
- EAG note approach to account for dose reductions is inconsistent and prefers to use RDI to model acquisition costs for all treatments for consistency
- EAG concerned about wastage if patients transition between different packs in event of a dose reduction

Company

- Conducted market research data on 2nd and 3rd line use of lorlatinib, that indicated [redacted] of patients had dose reduced from 2nd cycle
- Minimal wastage of 100mg tablets expected as dose reductions made following completion of a treatment cycle, and prescription amended to 25mg tablet strength if necessary

EAG comments

- Company's explanation sufficient for no additional wastage of 100mg tablets due to dose reductions
- Company didn't comment on EAG's preference using RDI to calculate acquisition costs across comparators
- Maintains RDI costing method used consistently for all treatments

Should the RDI costing method be used for all treatments?

Abbreviations: RDI, relative dose intensity

Partially resolved: Treatment beyond progression on lorlatinib is likely

Background

- Treatment beyond progression wasn't permitted in model (assumed time on treatment equal to PFS)
- EAG presented exploratory scenario using second-line study on lorlatinib (75.6% of patients continued to receive lorlatinib following progression, for median additional duration of 5.7 months)

Company

- Approximately 50% of patients treated beyond progression, for an average of 3 months (clinical advice)
- Likely same approach would be taken in first and second-line (clinical advice)
- Company explored range of exploratory scenarios

EAG comments

- Consider company's scenarios plausible and informative for committee discussion
- Company's approach differs from EAG (company's approach inclusive of assumption that treatment has an effect upon HRQoL independent of progression status using CROWN EQ-5D data)

Which exploratory scenario is most plausible?

#	Parameter varied
1	Treatment beyond progression (1.5 months in 1L and 3 months 2L)
2	Treatment beyond progression (3 months in 1L and 2L)
3	Treatment beyond progression (3 months in 1L and 5.7 months in 2L)
4	Treatment beyond progression (5.7 months in 1L and in 2L)

Abbreviations: PFS, progression-free survival; HRQoL, health-related quality of life; EQ-5D, EuroQol 5 dimensions; L, line

Summary of company and EAG base case assumptions

Table 10 Assumptions in company and EAG base case

Assumption	Company base case	EAG base case
PFS NMA	ALESIA excluded	Global NMA results (including ALESIA)
Health states	CNS-PD health state modelled	Removal of CNS PD health state
Utilities	Utilities derived from CROWN	Utilities derived from TA670
Drug acquisition costs	Dosing information for lorlatinib from CROWN, RDI method for comparators	RDI costing method used consistently for all treatments
Proportion of comparator patients going on to second-line lorlatinib	5% of patients would not be expected to receive lorlatinib following progression on alectinib and brigatinib	Proportion of comparator patients going on to second-line lorlatinib equal to the proportion of patients who received a subsequent anti-cancer therapy in CROWN after progression on lorlatinib [redacted]

The EAG also present an exploratory base case with what they consider to be a conservative set of assumptions that includes a treatment cap at 10 years, arm specific deaths as a proportion of PFS events, AE disutility correction & CROWN duration data and treatment beyond progression

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Abbreviations: CNS-PD, central nervous system progressed-disease; RDI, relative dose intensity; TA, technology appraisal; NMA, network meta-analysis

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

- Comparators alectinib and brigatinib have PAS discounts
- Subsequent treatment pemetrexed is subject to confidential commercial arrangements

Cost-effectiveness results and scenarios

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Company base case (including all discounts): ICER > £30,000/QALY

Exploratory scenarios applied to company base case:
Treatment beyond progression (1.5 months in 1L and 3 months 2L)
Treatment beyond progression (3 months in 1L and 2L)
Treatment beyond progression (3 months in 1L and 5.7 months in 2L)
Treatment beyond progression (5.7 months in 1L and in 2L)

EAG base case

- Global NMA HRs (including ALESIA)
- Removal of CNS PD health state
- TA670 utilities
- RDI costing method used consistently for all treatments
- Comparator patients progressing onto chemo vs lorlatinib based on CROWN

EAG base case ICERs > £30,000/QALY

EAG exploratory base case (conservative)

- Global NMA HRs (including ALESIA)
- Treatment effect cap at 10 years
- Arm-specific deaths as proportion of PFS events
- Removal of CNS PD health state
- TA670 utilities
- AE disutility correction & CROWN duration data
- RDI costing method used consistently for all treatments
- Comparator patients progressing onto chemo vs lorlatinib based on CROWN

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Abbreviations: L, line; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; CNS-PD, central nervous system progressed-disease; RDI, relative dose intensity; TA, technology appraisal; NMA, network meta-analysis; HR, hazard ratio; PFS, progression-free survival; AE, adverse event; PAS, patient access scheme

Cancer Drugs Fund

Due to the immaturity of OS data lorlatinib is considered to be a candidate for the CDF

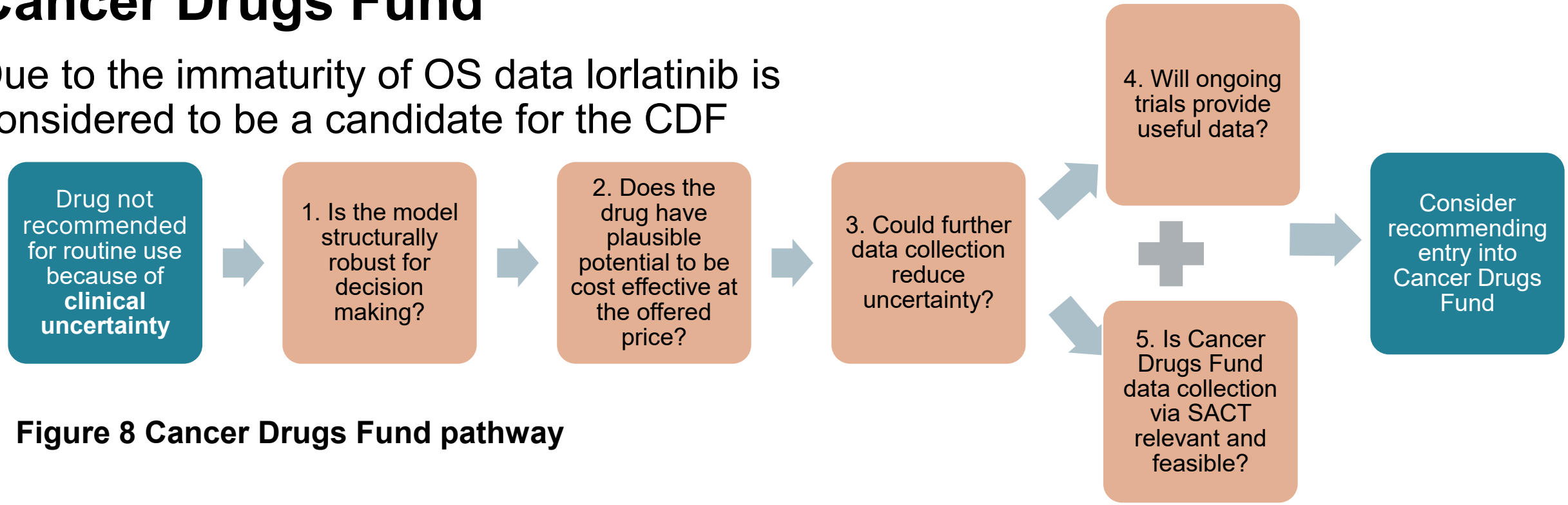

Figure 8 Cancer Drugs Fund pathway

- Company note that CROWN trial is still ongoing (final study completion date estimated December 2028)
- Company note that Interim and final data cuts for OS are planned for [redacted] and [redacted] which will reduce uncertainty around survival estimates for lorlatinib
- No further trials for lorlatinib in this indication are ongoing

Does lorlatinib meet the criteria to be considered for recommendation in the CDF? Is the CDF likely to address uncertainties associated with the appraisal?

Abbreviations: CDF, cancer drugs fund; SACT, Systemic Anti-Cancer Therapy; OS, overall survival

Feasibility of further data collection in CDF to resolve key uncertainties

Planned interim and final PFS & OS data cuts (and)

Figure 9 Comparison of PFS extrapolations – lorlatinib (based on company's model)

Table 11 CDF consideration

Uncertainty	Source of further data collection
OS estimates for lorlatinib	Could be informed by further data cuts from CROWN trial
Relationship between PFS and OS	Could be informed by further data cuts from CROWN trial
ECOG performance status	May be resolvable through SACT data
Treatment sequences	Not resolvable through data collection from CROWN
Baseline CNS metastases as a potential treatment effect modifier	EAG note it is unclear how additional data collection via the CDF could help to resolve this issue Company plan to conduct a Delphi panel on the proportion of people with CNS metastases

Abbreviations: CDF, cancer drugs fund; SACT, Systemic Anti-Cancer Therapy; OS, overall survival; PFS, progression-free survival; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group Performance Status

Resolved Issues

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Resolved: Death was not modelled as a PFS event

Company accept EAG's update to modelling error at technical engagement

Background

- Company didn't adjust health state transitions to reflect proportion of PFS events that were death in CROWN
- EAG noted this results in overestimation of patients remaining alive in model, inflating QALY outcomes
- EAG assumed the omission of death events to be a modelling error, and corrected the model
- EAG assumed that patients in PFS health state would experience death events at rate observed in CROWN and applied it to their base case

Company

- Accept the EAG's update to modelling error

EAG comments

- Considers this issue resolved

Abbreviations: PFS, progression-free survival; QALY, quality-adjusted life year

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Thank you.

Back up slides

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CROWN results: Adverse events (1)

Table 12 AEs (all cycles), SAS (DCO September 2021)

Variable	Lorlatinib (N=149)[a]	Crizotinib (N=142)[a]
All causalities		
Number of AEs	[redacted]	[redacted]
Patients with AEs, n (%)	[redacted]	[redacted]
Patients with SAEs, n (%)	[redacted]	[redacted]
Patients with maximum Grade 3 or 4 AEs, n (%)	[redacted]	[redacted]
Patients with maximum Grade 5 AEs, n (%)	[redacted]	[redacted]
Patients discontinued from study due to AEs, n (%)[b]	[redacted]	[redacted]
Patients discontinued study treatment due to AEs, n (%)[c]	[redacted]	[redacted]
Patients with dose reduced or temporary discontinuation due to AEs, n (%)	[redacted]	[redacted]
Treatment related		
Number of AEs	[redacted]	[redacted]
Patients with AEs, n (%)	[redacted]	[redacted]
Patients with SAEs, n (%)	[redacted]	[redacted]
Patients with maximum Grade 3 or 4 AEs, n (%)	[redacted]	[redacted]
Patients with maximum Grade 5 AEs, n (%)	[redacted]	[redacted]
Patients discontinued from study due to AEs, n (%)[b]	[redacted]	[redacted]
Patients discontinued study treatment due to AEs, n (%)[c]	[redacted]	[redacted]
Patients with dose reduced or temporary discontinuation due to AEs, n (%)	[redacted]	[redacted]

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a Patients evaluable for AEs. b Patients who had an AE record that caused study discontinuation. c Patients who had an AE record that caused treatment discontinuation

Abbreviations: DCO, data cut-off; SAE: serious adverse event; SAS: safety analysis set

Uncertainty in the new methods and processes : maintaining and updating our approach

Understanding and presenting uncertainty

- Improvements to ensure uncertainty is thoroughly characterised, clearly presented and fully understood

Considering uncertainty in decision making

- Retain critical consideration of uncertainty and decision risk
- Ensure no inappropriate barriers, through formalised flexibility with uncertainty

Maintain key principle: more caution when there is less certainty about the evidence

Low uncertainty, low decision risk = **more likely to recommend**	High uncertainty, high decision risk = **less likely to recommend**

Clarify and formalise flexibility: higher uncertainty may be considered when evidence generation is difficult:

- Rare diseases
- Populations including children
- Innovative and complex technologies