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

Slides for the public – contains no ACIC or CPAS information

**Technology appraisal committee D [16 March 2023]**

**Chair:** Megan John

**Lead team:** Matt Bradley, Ivan Koychev, Carole Pitkeathley

**External assessment group:** CRD and CHE Technology Assessment Group

**Technical team:** Ross Wilkinson, Lizzie Walker, Linda Landells

**Company:** Pfizer

# Key clinical issues from ACM1

**Recommendation:** Lorlatinib is not recommended, within its marketing authorisation, for treating anaplastic ALK-positive advanced NSCLC in adults who have not had an ALK inhibitor

**Table** Key clinical issues

| Issue | Committee's considerations | Updated by company? |
|---|---|---|
| Very few participants with an ECOG performance status score of 2 were recruited into the CROWN trial *(3.4)* | **Unresolvable uncertainty** – uncertain if CROWN evidence applicable to people with an ECOG of 2 | NA |
| Obsolete ALK inhibitor treatment sequences used in the CROWN trial *(3.5)* | **Unresolvable uncertainty** – comparator and subsequent treatments not in NHS practice | NA |
| Immature OS PFS data from CROW *(3.6)* | **Unresolvable uncertainty** | NA |
| Differences in the proportions with CNS metastases at baseline in trials included in the NMA *(3.8 and 3.9)* | **Unresolvable uncertainty** – baseline CNS metastases may affect prognosis and treatment effect | NA |
| Exclusion of the ALESIA study from the NMA used in the economic model *(3.7)* | Use global NMA (including ALESIA study) | YES |
| Incidence of grade ≥ 3 AEs with lorlatinib compared to other ALK inhibitors *(3.10)* | **Additional information requested –** safety profile may be different from other ALK TKIs → requested comparative analysis of grade 3 and 4 AEs | NO |

Abbreviations: AE, adverse event ALK, anaplastic lymphoma kinase; CNS, central nervous system; EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; NMA, network meta-analysis; OS, overall survival, PFS, progression free survival; TKI, Tyrosine Kinase Inhibitor

# Key cost-effectiveness issues from ACM1

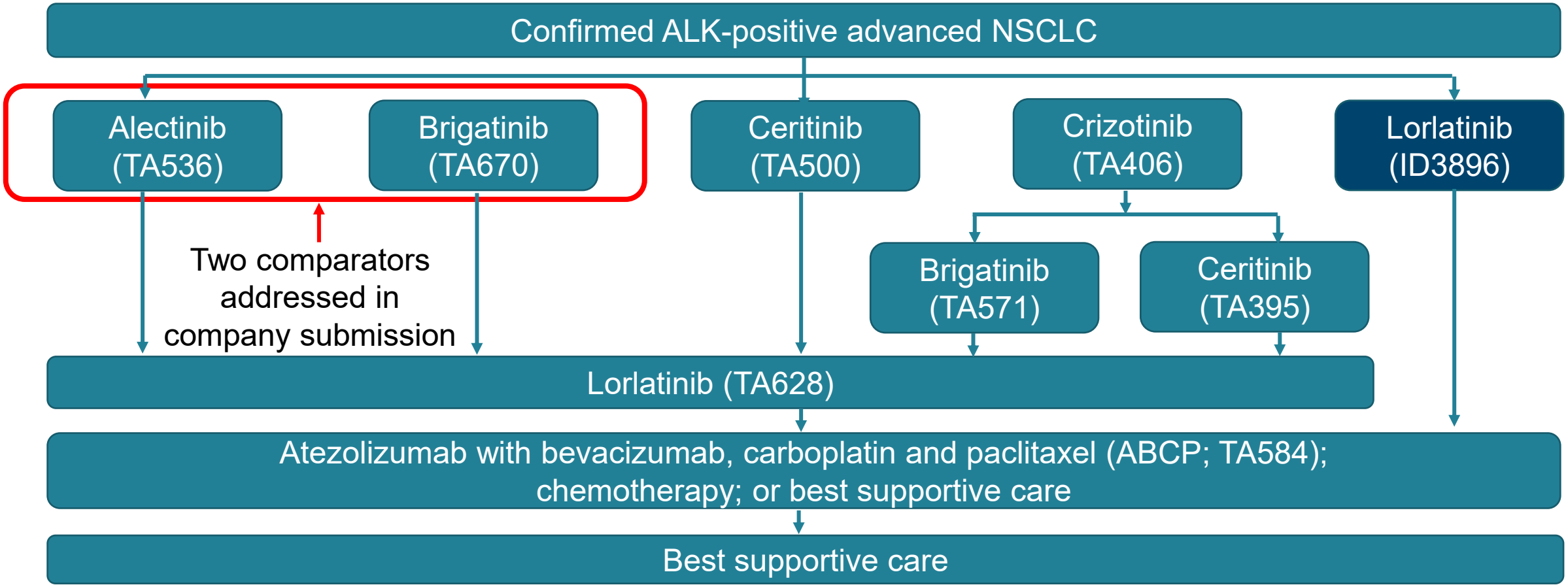
**Table** Key cost-effectiveness issues

| Issue | Committee's considerations | Updated by company? |
|---|---|---|
| PFS benefit is uncertain due to immaturity of CROWN data *(3.14)* | • Apply a treatment effect cap at 10 years<br>• **Unresolvable uncertainty remains** | YES |
| Insufficient data available to model CNS PD health state *(3.13)* | Remove the CNS PD health state | NO |
| Modelling treatment beyond progression on lorlatinib *(3.15)* | • Apply 5.7 months of treatment with lorlatinib post progression (1st and 2nd)<br>• Use [redacted] as proportion progressing to 2nd-line lorlatinib after brigatinib / alectinib | YES |
| HRQoL data from CROWN not reflective of real-world utilities *(3.17)* | Use TA670 utility values | YES |
| Dosing calculations *(3.18)* | Use RDI approach for lorlatinib | NO |
| OS benefit is uncertain due to immaturity of data from CROWN *(3.16)* | **Additional information requested –**<br>• analyses exploring other data sources for PPS on chemotherapy after 1st-line ALK TKIs<br>• analyses where risk of PPS is adjusted by CNS progression status | IN PART |

Abbreviations: ALK, anaplastic lymphoma kinase; CNS, central nervous system; EAG, external assessment group; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; NMA, network meta-analysis; OS, overall survival; PD, progressed disease; PPS, post-progression survival; RDI, relative dose intensity; TKI, tyrosine kinase inhibitor

# ALK-positive NSCLC treatment pathway

**Figure** Treatment pathway for people with ALK-positive advanced NSCLC in UK clinical practice

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

# Lorlatinib (Lorviqua, Pfizer)

**Table** 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<br>• MHRA marketing authorisation granted 23 September 2021<br>• Granted ORBIS designation by the MHRA |
| **Mechanism of action** | • Lorlatinib inhibits the ALK and ROS1 receptor tyrosine kinases, acting against a range of ALK resistant mutations<br>• 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<br>• A patient access scheme is available for lorlatinib<br>  • Updated PAS submitted ahead of ACM2 → subject to a positive recommendation for the whole population in this appraisal |

Abbreviations: ACM, appraisal committee meeting; ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; MHRA, Medicines and Health Regulatory Agency; PAS, patient access scheme

# Clinical effectiveness recap

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# Key clinical trial

## Overall survival data from CROWN trial are immature

**Table** 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]<br>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 2025 and 2028

*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 results: progression-free survival

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

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

Comparison versus crizotinib (stratified analysis):

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

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



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

# NMA results

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

- No head-to-head studies identified directly comparing lorlatinib to alectinib and brigatinib, so standard Bayesian NMA conducted to assess relative efficacy of lorlatinib vs comparators
- Fixed effects model used for analyses of PFS and OS
- At ACM1, committee preferred the NMA that included ALESIA → company now include in its base case

**Figure** PFS and OS resulting network diagram

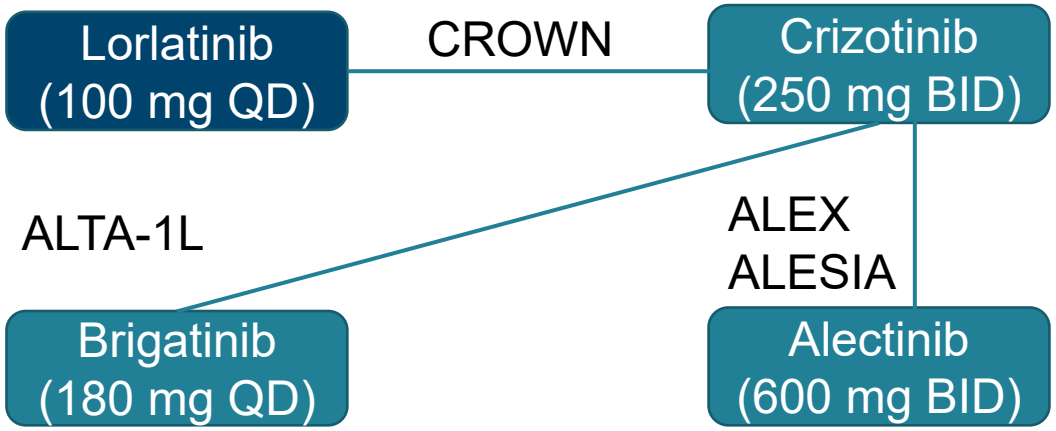


**Table** PFS/OS relative effect of lorlatinib compared with all treatments (fixed effects)

| | Treatment | HR (95% CrI) |
|---|---|---|
| PFS Sept 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] for both comparisons (March 2020 DCO)
- OS data from CROWN still very immature, therefore no conclusions could be drawn from this analysis

NICE *Excludes ALESIA

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

# Cost effectiveness recap

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# Company's model overview

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

Technology affects **costs** by:

- Increasing 1st-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

**Figure** Model structure

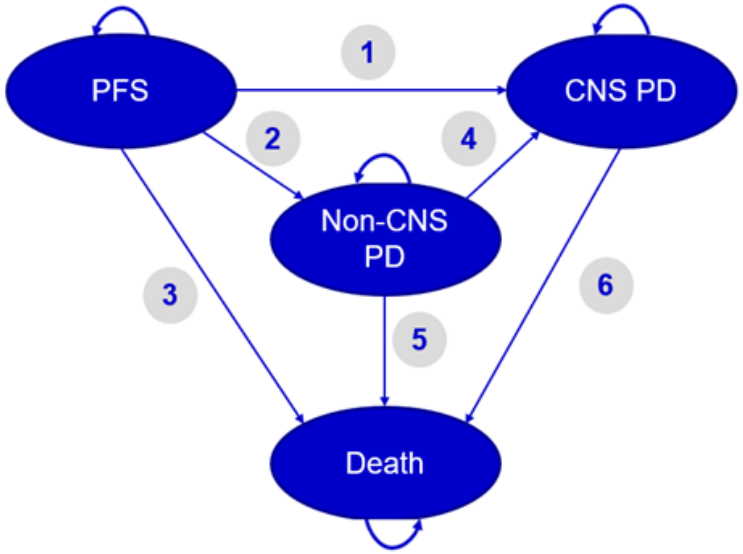


**Table** Evidence sources for model transitions

| Transition | Data source | Definition |
|---|---|---|
| 1 | CROWN | IC-TTP |
| 2 | CROWN | Extracranial progression |
| 3 | CROWN | Progression events which were death |
| 4 | CROWN | IC-PD after overall EC-PD |
| 5 | PROFILE 1005/ Study 1001 | Overall survival after 1L treatment |
| 6 | PROFILE 1005/ Study 1001 | Overall survival after 1L treatment |



Abbreviation: 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

# Response to consultation

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# Consultation responses (1)

## Consultation comments

Comments received from:

- Pfizer UK (company – manufacturer of lorlatinib)
- Takeda UK (company – manufacturer of brigatinib)
- ALK Positive UK (patient group)

## Pfizer UK

- Highlighted that lorlatinib has received ORBIS designation
- Suggested that:
  - Consequences of decision error are low given the limited budget impact
  - Lorlatinib may be a candidate for the CDF
- Responded to the committees concerns that PFS and OS data from CROWN is immature
- Provided:
  - Updated model incorporating some of the committee's preferred assumptions
  - Justification where the committee's preferred assumptions were not incorporated in the model

Abbreviations: ALK, anaplastic lymphoma kinase; CDF, Cancer Drugs Fund; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival

# Consultation responses (2)

## Takeda UK

- Identified a factual inaccuracy and suggested a change to the guidance to better reflect comments made by patient experts at ACM1
- Agreed with the committee that a NMA assessing lorlatinib's treatment effect on grade 3/4 AEs compared with other ALK TKIs should be conducted
- Encouraged the committee to consider the clinical and cost implications of grade 3/4 AEs

## ALK Positive UK

- Was concerned that the draft guidance may imply that there are no benefits to lorlatinib being used in the 1st line setting
- Suggested that patients presenting with multiple brain metastases may benefit from a TKI with the highest brain penetration and currently don't have that option
- Stated it would like to see lorlatinib available for the 1st line therapy as well as its current position (2nd line)

Abbreviations: ACM, appraisal committee meeting; AE, adverse events; ALK, anaplastic lymphoma kinase; NMA, network meta-analysis; TKI, tyrosine kinase inhibitor

# Committee preferred assumptions and conclusions

## Company adopted most of the committee's preferred assumptions

| Committee preference at ACM1 | Updated by company | EAG comments |
|---|---|---|
| Use global NMA (include ALESIA) | Yes | - |
| Remove the CNS PD health state | No | CNS PD state should be removed |
| Apply a treatment effect cap at 10 years | Yes | - |
| • 1st and 2nd line lorlatinib 5.7 months post progression<br>• Proportion progressing to 2nd-line lorlatinib after brigatinib/alectinib ([redacted]) | Yes – also included 3 months treatment beyond progression for alectinib and brigatinib | Corrected company's approach for modelling ToT - Also included 3 months treatment beyond progression for alectinib and brigatinib included into base case |
| Use TA670 utility values | Yes | - |
| Use RDI approach | No | RDI approach is appropriate |
| Model arm-specific death as a proportion of PFS | Yes | - |
| AE disutility from literature, AE durations from CROWN where available | Partly – AE disutility from TA670 and literature, AE durations from CROWN where available | - |



Abbreviations: ACM, appraisal committee meeting; AE, adverse events; CNS, central nervous system; EAG, external assessment group; NMA, network meta-analysis; PD, progressed disease; PFS, progression free survival; RDI, relative dose intensity; ToT, time on treatment

# Committee recommendations for further analyses

Company did some of the committee's recommendations for further analyses

| Committee preference at ACM1 | Updated by company | EAG comments |
|---|---|---|
| Requested comparative analysis of grade 3 and 4 AEs | No | - |
| Requested analyses exploring other data sources for PPS on chemotherapy after 1st-line ALK TKIs | Yes – performed a targeted literature search for PPS data. Identified 2 potential alternative sources but less relevant than current evidence sources | Sources look less relevant than those used previously |
| Requested analyses where risk of PPS is adjusted by CNS progression status | No | - |



Abbreviations: ACM, appraisal committee meeting; AE, adverse events; ALK, anaplastic lymphoma kinase; CNS, central nervous system; EAG, external assessment group; PPS, post-progression survival; TKI, tyrosine kinase inhibitor;

# Committee discussion at ACM2

| Parameter | Key question | Scenarios | ICER impact | Committee preference |
|---|---|---|---|---|
| CNS PD health state | Should the CNS PD health state be removed? | • Yes<br>• No | Large  | ? |
| Drug acquisition costs | Which costing method should be used? | • Dosing information for lorlatinib from CROWN, RDI for comparators<br>• RDI used consistently for all treatments | Small  | ? |
| Uncertainty in PFS / OS | Is committee happy to accept the uncertainty? | | Unknown  | ? |
| CDF | Is lorlatinib suitable for the CDF? | • Yes<br>• No | | ? |

Abbreviations: ACM, appraisal committee meeting; CDF, cancer drugs fund; CNS, central nervous system; PD, progressed disease; PFS, progression free survival; RDI, relative dose intensity; OS, overall survival; ICER, incremental cost-effectiveness ratio; ToT, time on treatment

# Key issue: Modelling the CNS PD health state (1)

The company continues to use a 4-state model in its base case

## Committee comments at ACM1

- CNS PD health state may be more severe than the non-CNS PD health state
- Insufficient data to inform the transition to the CNS PD health state
- Removing the CNS PD health state would improve transparency and avoid introducing uncertainty

## Company response to DGD

- **No change to ACM1 base case –** Sufficient data from CROWN to inform model transitions → enables benefits of lorlatinib in delaying CNS progression to be reflected
- In CROWN, overall PD and intracranial PD were independent events and investigator could choose to continue treatment after PD

**Table** Reported IC-PD and Overall PD by BICR (Full Analysis Set) – 36.7 months follow-up

| n (%) | Lorlatinib (n=149) | Crizotinib (n=147) |
|---|---|---|
| IC-PD and Overall PD/Death reported within 7 days | [redacted] | [redacted] |
| IC-PD reported at least 7 days before Overall PD/Death | [redacted] | [redacted] |
| **IC-PD reported at least 7 days after Overall PD/Death** | [redacted] | [redacted] |
| IC-PD reported without Overall PD/Death | [redacted] | [redacted] |

- Prevention of CNS PD is a substantial benefit of lorlatinib and it is important that it is captured in the model

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Abbreviations: ACM, appraisal committee meeting; BICR, blinded independent central review; CNS, central nervous system; DGD, draft guidance document; IC-PD, intracranial progressed disease; PD, progressed disease

# Key issue: Modelling the CNS PD health state (2)

## EAG believe current model structure can not model clinically plausible CNS benefit

**EAG comments**

**Key transitions are not captured in the model**

- Model does not allow transitions from the non-CNS-PD health state into the CND-PD health state
- Model does not adjust risk of mortality between non-CNS-PD and CNS-PD health states

**Not appropriate to assume the IC effect size of lorlatinib vs crizotinib is unique to lorlatinib**

- CNS-PFS curves for alectinib and brigatinib obtained using the IC-TTP on crizotinib in CROWN → alectinib and brigatinib have been shown to have better IC activity than crizotinib

**Not appropriate to assume CNS-PFS and PFS treatment effects are equal**

- CNS-PFS curves are obtained by applying the PFS HRs to the crizotinib IC-TTP curve
- Evidence suggests CNS-PFS efficacy is not equal to PFS efficacy
- Approach may underestimate the benefits of comparators in delaying CNS progression

**Table** CNS-PFS and PFS HRs from trial

| | CNS-PFS HR | PFS HR | Source |
|---|---|---|---|
| Lorlatinib vs crizotinib | [redacted] | [redacted] | CROWN |
| Alectinib vs crizotinib (with baseline CNS metastases) | 0.18 | 0.40 | ALEX |
| Alectinib vs crizotinib (without baseline CNS metastases) | 0.14 | 0.51 | ALEX |

- Scenario using naive CNS-PFS HR for alectinib vs crizotinib (ALEX) → reduces incremental QALY gain for lorlatinib vs company base case → incremental QALY gain for lorlatinib only [redacted] QALYs higher than when the CNS-PD health state is removed

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Abbreviations: CNS, central nervous system; EAG, external assessment group; HR, hazard ratio; IC, intracranial; IC-TTP, intracranial-time to progression; PD, progressed disease; PFS, progression free survival; QALY, quality-adjusted life year

# Key issue: Modelling the CNS PD health state (3)

## EAG believe CNS PFS transition fail to account for baseline CNS metastases

**EAG comments**

**Subgroups with and without CNS metastases should be modelled separately**

- Majority of IC progressions occur in the subgroup with CNS metastases at baseline
- Risks of IC progressions in the subgroup with CNS metastases at baseline may follow a different functional form than in the subgroup without CNS metastases at baseline

**Not appropriate to assume proportional hazards**

- The crizotinib IC-TTP curve assumes a constant event rate → evidence suggests this is not the case for alectinib
- Assuming a constant event rate results in clinically implausible predictions of the number of patients with CNS metastases at baseline experiencing CNS PD on alectinib

**Overall, EAG disagrees with use of 4-state model given current data availability.** If 4 state model is used:

- Not appropriate to assume CNS-PFS and PFS treatment effects are equal. May be more appropriate to use CNS TTP data
- Not appropriate to assume same risks in people with and without CNS metastases at baseline
- Transitions have not been modelled appropriately

Has the committee seen any information to change their position that the CNS PD health state should be removed?



Abbreviations: CNS, central nervous system; EAG, external assessment group; HR, hazard ratio; IC-TTP, intracranial-time to progression; PD, progressed disease; PFS, progression free survival; QALY, quality-adjusted life year

# Key issue: Dosing method for lorlatinib

Company and EAG preferences unchanged and no new evidence was provided

## Committee comments at ACM1

- RDI approach was most appropriate and aligned with methods used in previous appraisals

## Company response to DGD

- **No change to ACM1 base case**
- Clinical experts at ACM1 confirmed all people starting on 100mg is reflective of NHS clinical practice
- If required dose reductions occur at the end of a cycle
- Dosing data from CROWN reflects clinical practice, aligned with clinical expert opinion and the model can incorporate it accurately.

## EAG comments

- Acknowledge CROWN dosing data best represents real dose reductions and missed doses savings
- Company approach results in lower average cost of treatment for lorlatinib
- Equivalent dosing data from alectinib and brigatinib trials could show a similar reduction in cost
- Maintains RDI costing method should be used consistently for all treatments
  - RDI: best reflects difference in total costs between lorlatinib, alectinib and brigatinib
  - CROWN data: provides most accurate costs for lorlatinib

Has the committee seen any new evidence to change their opinion that the RDI approach is a more appropriate method for calculating dosing costs than using CROWN data?

Abbreviations: ACM, appraisal consultation meeting; DGD, draft guidance document; RDI, relative dose intensity

# Key issue: Uncertainty in PFS

Evidence suggests lorlatinib is associated with an improvement in PFS

## Committee comments at ACM1

- CROWN is ongoing and the follow up time was short → PFS data is immature
- PFS data is associated with a high level of uncertainty → taken into account during decision making

## Company response to DGD

- Immature PFS data for lorlatinib from CROWN data cut shows efficacy of lorlatinib in preventing progression
- Clinical experts at ACM1 considered PFS of 2 to 3 years clinically meaningful
- Modelled lorlatinib median PFS (53.2 months) aligns with clinical opinion from advisory board (4 to 5 years)
- Reiterated evidence shows improved PFS for lorlatinib vs alectinib and brigatinib

## EAG comments

- Available data supports significantly improved PFS on lorlatinib relative to alectinib and brigatinib
- Magnitude of PFS benefit is uncertain → will become clearer with further data cuts from CROWN



Abbreviations: ACM, appraisal committee meeting; DGD, draft guidance document; EAG, external assessment group; PFS, progression free survival

# Key issue: Uncertainty in OS

It is possible an extension to PFS could lead to an extension of OS

## Committee comments at ACM1

- CROWN is ongoing and the follow up time was short → OS data is immature
- KM curves diverged, suggesting an advantage for lorlatinib, but then later reconverged

## Company response to DGD

- OS HR suggests lorlatinib reduced risk of death compared to crizotinib but was not statistically significant (HR 0.72; 95% CI: 0.41 to 1.25; March 2020 DCO)
- If recommended in the CDF, re-submission would use OS data from future CROWN DCO (expected 2025)

## EAG comments

- Plausible a significant extension to PFS would lead to an extension to OS
- ACM1 clinical experts explained it is plausible post-progression survival is unaffected by prior treatments
- Even with the 10 year treatment effect cap, modelled PFS benefit produces a significant OS benefit vs comparators
- Reiterated that OS data from CROWN is confounded by treatments received post progression which are not available in NHS practice

Abbreviations: ACM, appraisal committee meeting; CDF, Cancer Drugs Fund; DCO, data cut off; DGD, draft guidance document; EAG, external assessment group; HR, hazard ratio; KM, Kaplan-Meier; OS, overall survival; PFS, progression free survival

# 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
- Company and EAG ICERs are above the threshold normally considered as an effective use of NHS resources

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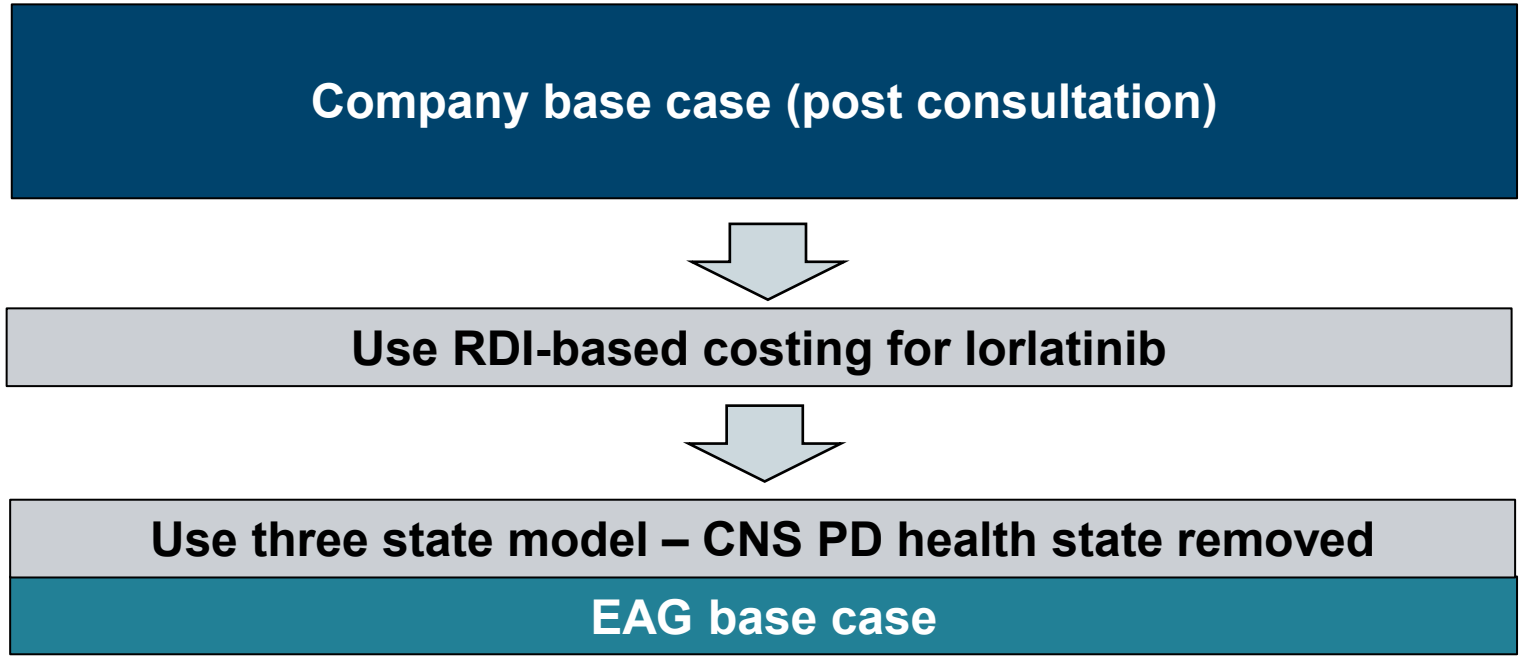
# Cost-effectiveness results and scenarios




Abbreviations: CNS, central nervous system; EAG, external assessment group; PD, progressed disease; RDI, relative dose intensity

# Managed access

## Criteria for a managed access recommendation

**The committee can make a recommendation with managed access if:**

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

# Cancer Drugs Fund

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

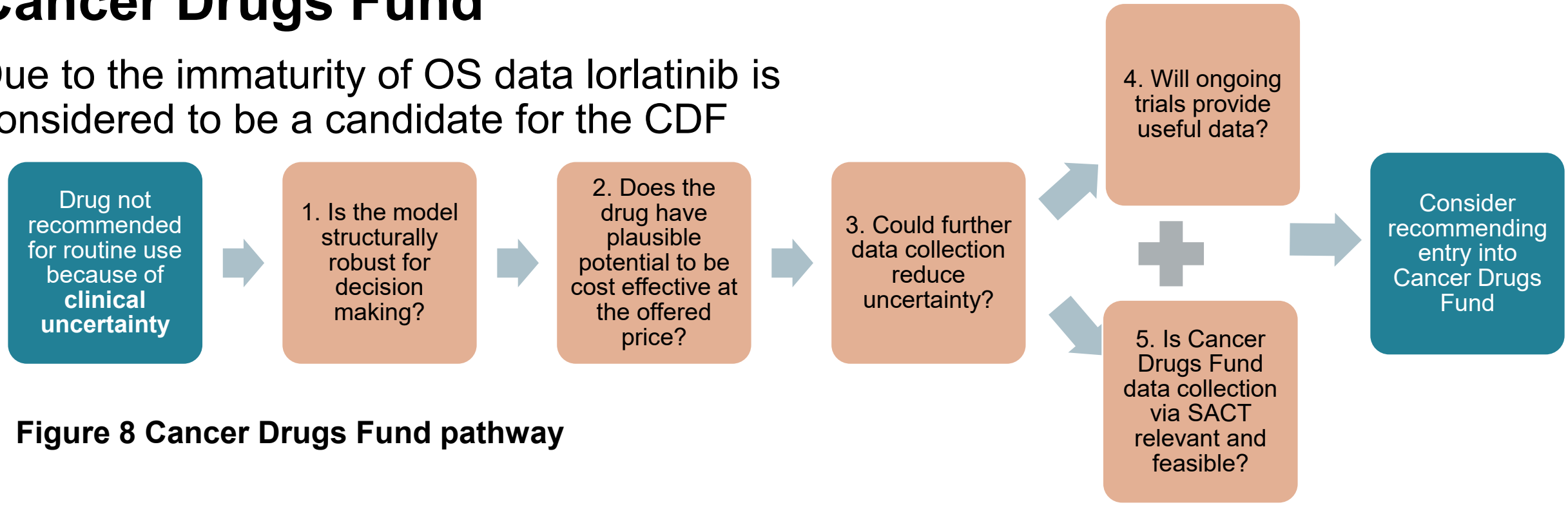



**Figure 8 Cancer Drugs Fund pathway**

- 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 2025 and 2028 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

**Figure** Comparison of PFS extrapolations – lorlatinib

**Table** CDF consideration

| Uncertainty | Source of further data collection |
|---|---|
| OS estimates for lorlatinib | Could be informed by further data cuts from CROWN trial → EAG believe CROWN OS data is heavily confounded |
| 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<br>Company plan to conduct a Delphi panel on the proportion of people with CNS metastases |

Abbreviations: CDF, Cancer Drugs Fund; DCO, data cut off; SACT, Systemic Anti-Cancer Therapy; OS, overall survival; PFS, progression-free survival; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group Performance Status

# Committee discussion at ACM2

| Parameter | Key question | Scenarios | ICER impact | Committee preference |
|---|---|---|---|---|
| CNS PD health state | Should the CNS PD health state be removed? | • Yes<br>• No | Large  | ? |
| Drug acquisition costs | Which costing method should be used? | • Dosing information for lorlatinib from CROWN, RDI for comparators<br>• RDI used consistently for all treatments | Small  | ? |
| Uncertainty in PFS / OS | Is committee happy to accept the uncertainty? | | Unknown  | ? |
| CDF | Is lorlatinib suitable for the CDF? | • Yes<br>• No | | ? |

Abbreviations: ACM, appraisal committee meeting; CDF, cancer drugs fund; CNS, central nervous system; PD, progressed disease; PFS, progression free survival; RDI, relative dose intensity; OS, overall survival; ICER, incremental cost-effectiveness ratio; ToT, time on treatment

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# Thank you.