# Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (Review of TA909)

**PART 1**
For screen – confidential information redacted

**Technology appraisal committee D [12 March 2025]**

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**Company:** Pfizer

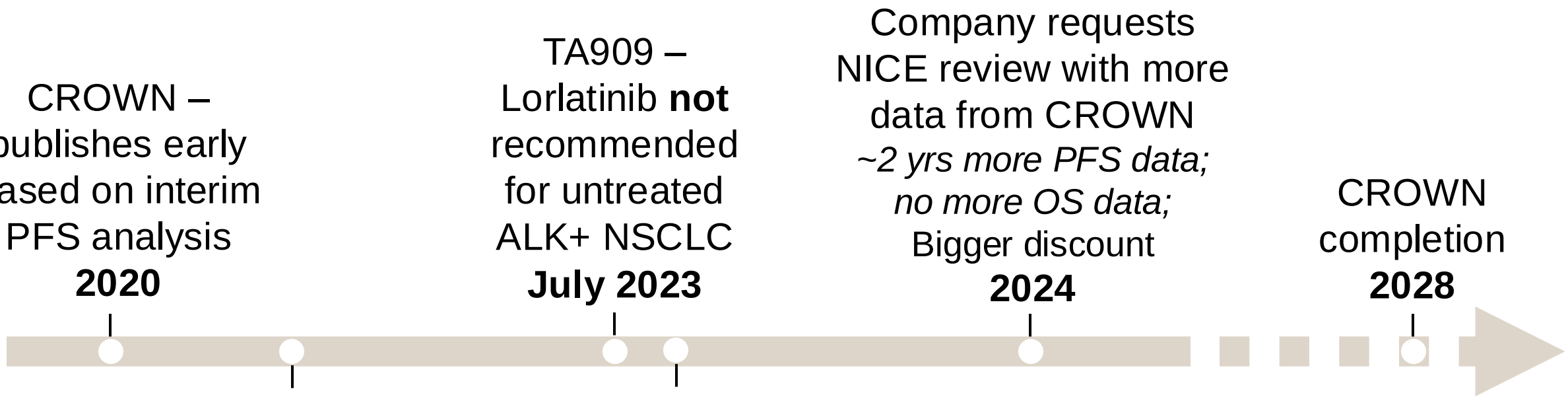
# Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (Review of TA909)

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

NICE National Institute for Health and Care Excellence

# Lorlatinib timeline – previously appraised – not recommended

*More PFS but not OS data; Key trial CROWN against crizotinib not relevant comparator*




**NICE approved lorlatinib 2nd line**

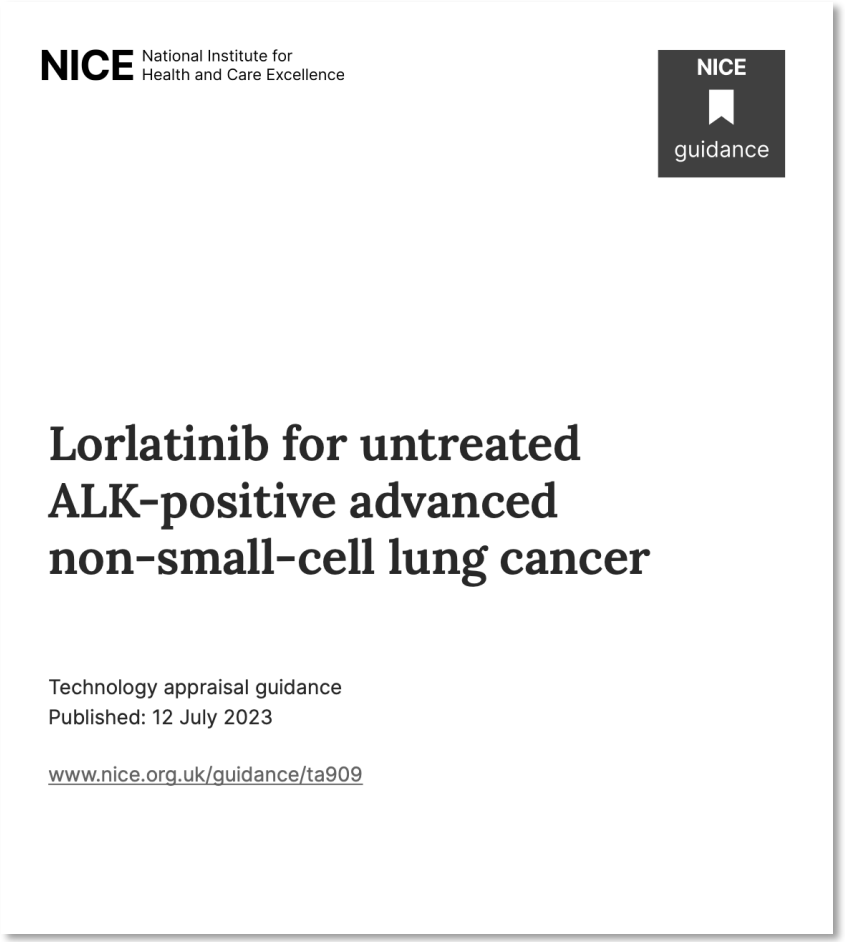
- TA628 (2020) – ALK+ NSCLC

ALK, anaplastic lymphoma kinase; ICER, incremental cost-effectiveness threshold; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

# Previous appraisal (TA909) – same decision problem

Committee conclusions:

- Current NHS practice – alectinib or brigatinib 1st line, then lorlatinib 2nd line and chemotherapy 3rd line
- Neither comparator crizotinib nor 2nd line treatments in CROWN used in NHS
- Both PFS and OS immature
- Indirect comparison OK if 'global' network used
- Treatment-effect cap at 10 years
- Whether PFS associated with OS 'very uncertain'
- 3 months of treatment beyond progression for alectinib and brigatinib
- Adjust post progression survival for CNS disease

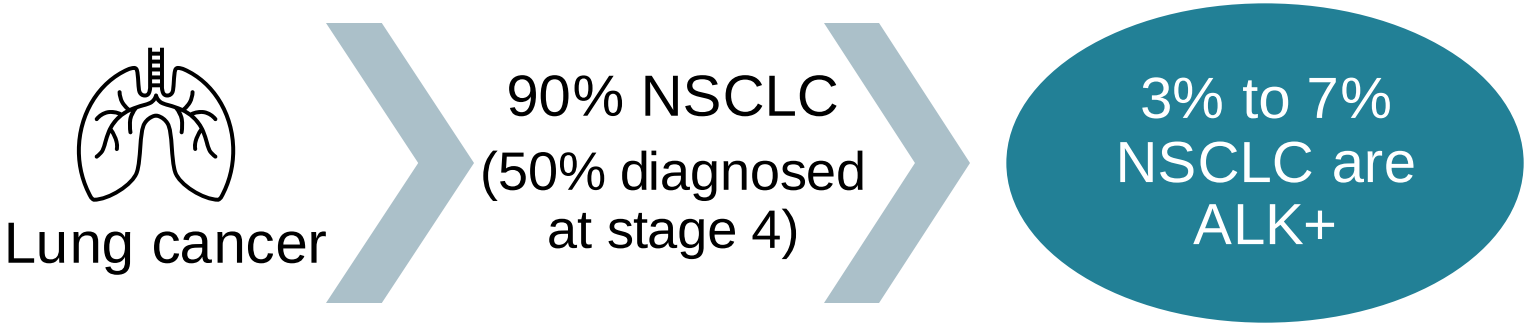



NICE ALK, anaplastic lymphoma kinase; CNS, central nervous system; OS, overall survival; PFS, progression-free survival.

# Disease background

## Epidemiology, classification, causes

- In 2024, ≈ 39,097 people diagnosed with NSCLC in England & Wales




## Prognosis and symptoms

- Often advanced disease at diagnosis
- 5-year survival <10%
- Poor quality of life – pain, breathlessness, persistent cough
- Brain metastases 20 to 40% – drowsiness, severe headaches, confusion, care needs

NICE ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

# Patient and clinical perspectives



Experts say lorlatinib has impressive PFS results and manageable toxicities

**ALK Positive UK and Roy Castle Lung Foundation**

- Symptoms debilitating and prognosis poor
- Patients often < 50 years old with active lives + young families
- Lorlatinib promising delays progression + affects brain metastases
- Need for additional, more effective treatments

*'Increase in PFS with lorlatinib is seen as a game-changer'*

**British Thoracic Oncology Group**

- Main aim of treatment is to prolong survival, reduce tumour size
- Control of metastatic disease in central nervous system remains a key outcome for clinicians and patients – vital for quality of life
- Different side effects with lorlatinib than with current standard care, but not more difficult to manage

*'Lorlatinib PFS benefit is one of the most pronounced and impressive seen in solid tumours'*

NICE PFS, progression-free survival.

# Equality considerations

**Company**

- Some underserved communities and ethnic/socioeconomic groups have later diagnosis and worse outcomes, this likely includes those with ALK+ advanced NSCLC

**Patient organisations**

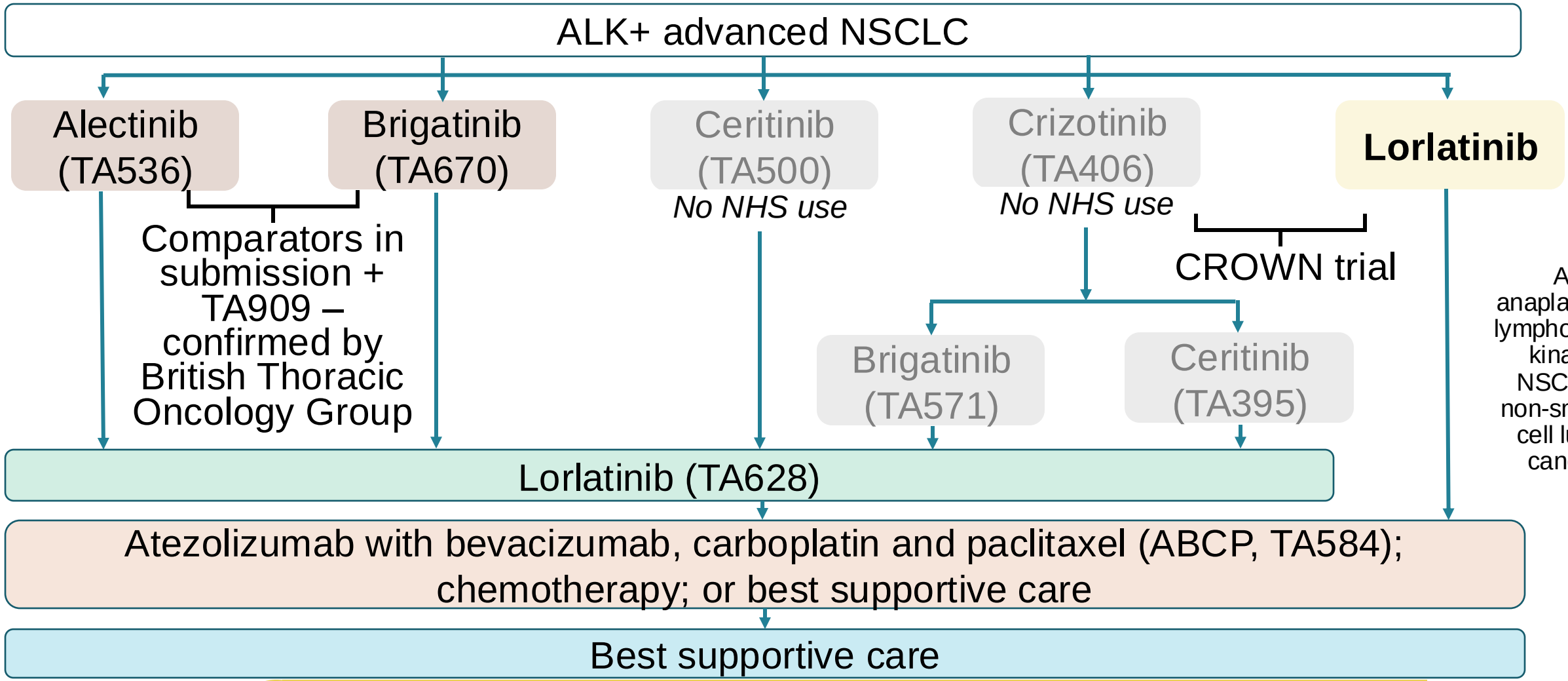
- Inequitable access in UK – lorlatinib available in Scotland



ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

# Treatment pathway

*People can get loratinib 1st line (this appraisal) or 2nd line after alectinib or brigatinib*
*No trial evidence of lorlatinib compared to alectinib or brigatinib*




ALK, anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer.

What is(are)the most appropriate comparator(s) for lorlatinib?

# Lorlatinib (Lorviqua®, Pfizer)

| | |
|---|---|
| **Marketing authorisation** | • Adults with ALK+ advanced NSCLC not previously treated with an ALK inhibitor |
| **Other indications** | • 2nd line – adults disease progressed after prior ALK inhibitor |
| **Mechanism of action** | • Inhibits ALK and ROS1 receptor tyrosine kinases, acts against a range of ALK resistant mutations |
| **Duration** | • '..as long as the patient is deriving clinical benefit from therapy without unacceptable toxicity.' |
| **Administration** | • 100 mg orally once daily |
| **Price** | • List price:<br>  ○ £5,283 per 30 x 100 mg tablets<br>  ○ £7,044 per 120 x 25 mg tablets<br>• A patient access scheme is available |

When would people stop taking lorlatinib in the NHS?

NICE ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; ROS proto-oncogene 1

# Key issues and uncertainties previous appraisal (TA909)

Key issues remain unresolved in this appraisal

| | This appraisal |
|---|---|
| CROWN 2nd line and beyond treatments do not reflect NHS | **Remain key issues** |
| CROWN immature overall survival | |
| Extrapolating progression-free survival | |
| Modelling post-progression survival | |
| Utility values | |
| CROWN immature progression-free survival | No longer key issues |
| CROWN differences in CNS metastases with other trials | |
| CNS metastases as modifier of treatment effect | |
| No network meta-analysis for adverse events | |
| Linking non-CNS and CNS progressed health states | |
| Modelling relative effect of lorlatinib on CNS progression | |

**NICE** CNS, central nervous system.

*Additional key issues for this appraisal listed on slide 11*

# Key issues – Evidence Assessment Group

| Issues | ICER impact |
|---|---|
| **Clinical effectiveness issues** | |
| Relevant comparator in NHS practice | N/A |
| Generalisability of treatment sequences in trials to NHS practice | Unknown |
| Immature overall survival data from CROWN | Unknown |
| Validity of overall survival estimates from network meta-analysis | Unknown |
| **Cost-effectiveness issues** | |
| Accounting for treatment sequences | Unknown |
| Inconsistent model structure | Small |
| Time on treatment and treatment beyond progression | Medium |
| Survival extrapolation | Medium |
| Waning of relative treatment effect over time | Medium |
| Utility values | Small |
| Implementing patient access scheme discount for lorlatinib | Small |

ICER, incremental cost-effectiveness ratio.

# Lorlatinib for untreated ALK-positive advanced non-small-cell lung cancer (Review of TA909)

- ❑ Background and key issues
- ✓ **Clinical effectiveness**
- ❑ Modelling and cost effectiveness
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- ❑ Summary

NICE National Institute for Health and Care Excellence

# Key clinical trial – CROWN

| | |
|---|---|
| **Design** | Phase 3, multicentre, open-label, randomised trial |
| **Population** | • Adults advanced ALK+ NSCLC<br>• No previous systemic treatment |
| **Intervention** | Lorlatinib 100 mg, oral 1x daily |
| **Comparator** | Crizotinib 250 mg, oral 2x daily – *not comparator in model for NHS* |
| **Treatment duration** | Median 62 months; treatment beyond progression permitted |
| **Median follow-up** | Lorlatinib PFS: 60.2 months; crizotinib PFS: 55.1 months<br>Lorlatinib OS: 20.0 months; crizotinib OS; 19.8 months |
| **1° outcome** | PFS based on **independent** assessment |
| **Key 2° outcomes** | Overall survival, PFS **investigator** assessment, intracranial outcomes, adverse effects, quality of life |
| **Locations** | 104 sites in 23 countries [3 UK sites] |
| **Used in model?** | Yes (but not with crizotinib as comparator) |

NICE

ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

# CROWN primary outcome: Progression-free survival – independent assessment

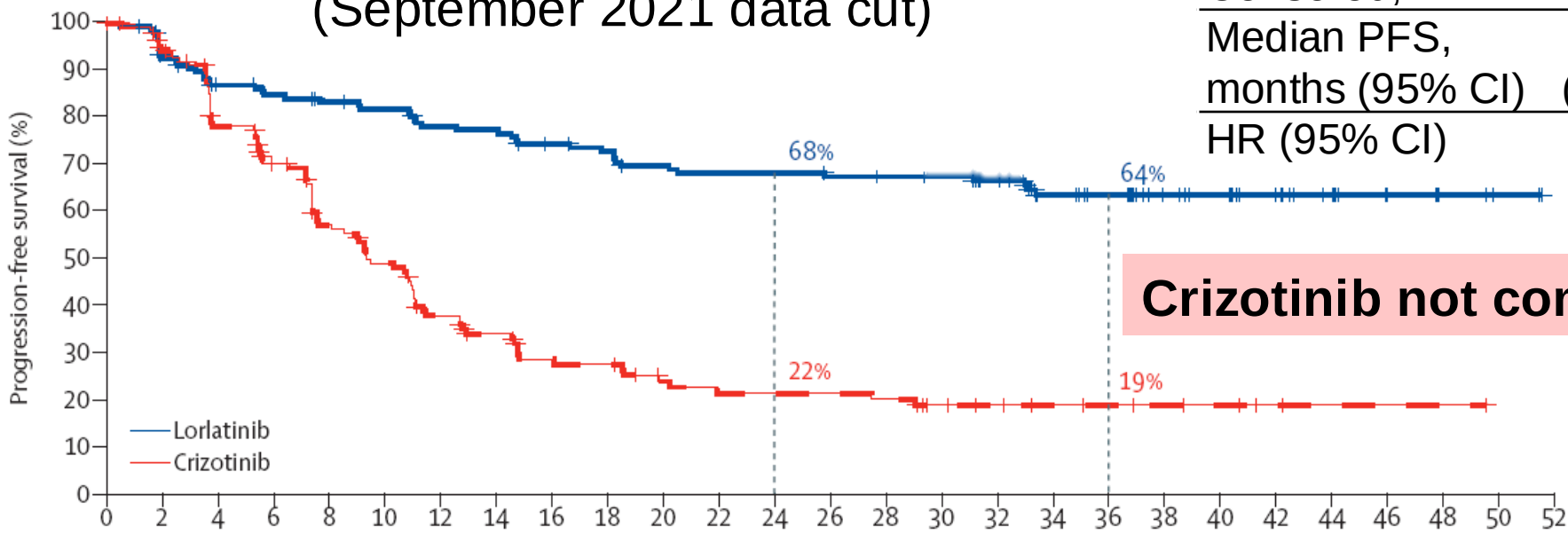
**Presented in TA909 – Sept 21 data cut**

Statistically and clinically significant improvement in PFS

| | Lorlatinib (n=149) | Crizotinib (n=147) |
|---|---|---|
| Events, n | 49 | 92 |
| Censored, n | 100 | 55 |
| Median PFS, months (95% CI) | NR (NR to NR) | 9.3 (7.6 to 11.1) |
| HR (95% CI) | 0.27 (0.18 to 0.39) | |

## PFS (independent assessment)

(September 2021 data cut)




Number at risk (number censored)

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lorlatinib | 149 (0) | 133 (5) | 122 (8) | 118 (9) | 114 (11) | 111 (12) | 105 (13) | 104 (13) | 98 (15) | 95 (16) | 90 (17) | 88 (17) | 88 (17) | 86 (18) | 85 (19) | 83 (21) | 72 (31) | 55 (45) | 50 (50) | 34 (66) | 31 (69) | 23 (77) | 15 (85) | 7 (93) | 4 (96) | 2 (98) | 0 (100) |
| Crizotinib | 147 (0) | 126 (13) | 100 (18) | 85 (23) | 64 (29) | 54 (30) | 40 (32) | 33 (35) | 26 (37) | 25 (37) | 19 (40) | 17 (40) | 17 (40) | 17 (40) | 16 (40) | 11 (44) | 9 (46) | 7 (48) | 6 (49) | 5 (50) | 4 (51) | 2 (53) | 1 (54) | 1 (54) | 1 (54) | 0 (55) | 0 .. |

**Crizotinib not comparator in appraisal**

## Independent vs. investigator PFS (%)

| | Lorlatinib | | Crizotinib | |
|---|---|---|---|---|
| | IND | INV | IND | INV |
| 24m | 68 | 70 | 22 | 15 |
| 36m | 64 | 65 | 19 | 10 |

NICE

CI, confidence interval; HR, hazard ratio; IND, independent, INV, investigator; NR, not reported; PFS, progression-free survival.

New data – Oct 2023 data cut

# CROWN secondary outcome: Progression-free survival – investigator assessment

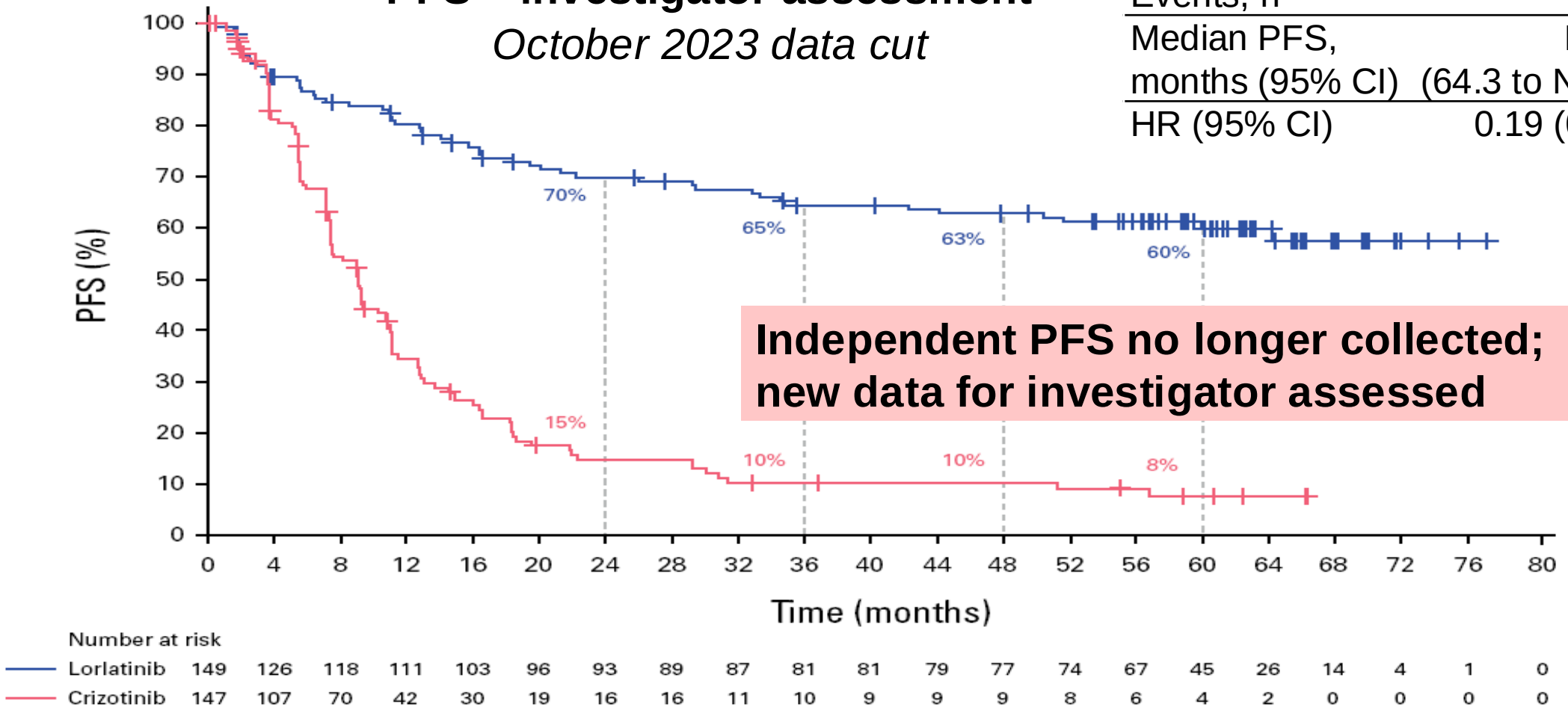
Improvement in PFS, but not as defined in primary endpoint

| | Lorlatinib (n=149) | Crizotinib (n=147) |
|---|---|---|
| Events, n | 55 | 115 |
| Median PFS, months (95% CI) | NR (64.3 to NR) | 9.1 (7.4 to 10.9) |
| HR (95% CI) | 0.19 (0.13 to 0.27) | |

Hazard ratio unchanged from previous cut (investigator assessed)

## PFS – investigator assessment

*October 2023 data cut*




**Independent PFS no longer collected; new data for investigator assessed**

NICE

CI, confidence interval; HR, hazard ratio; NR, not reported; PFS, progression-free survival.

New data – Oct 2023

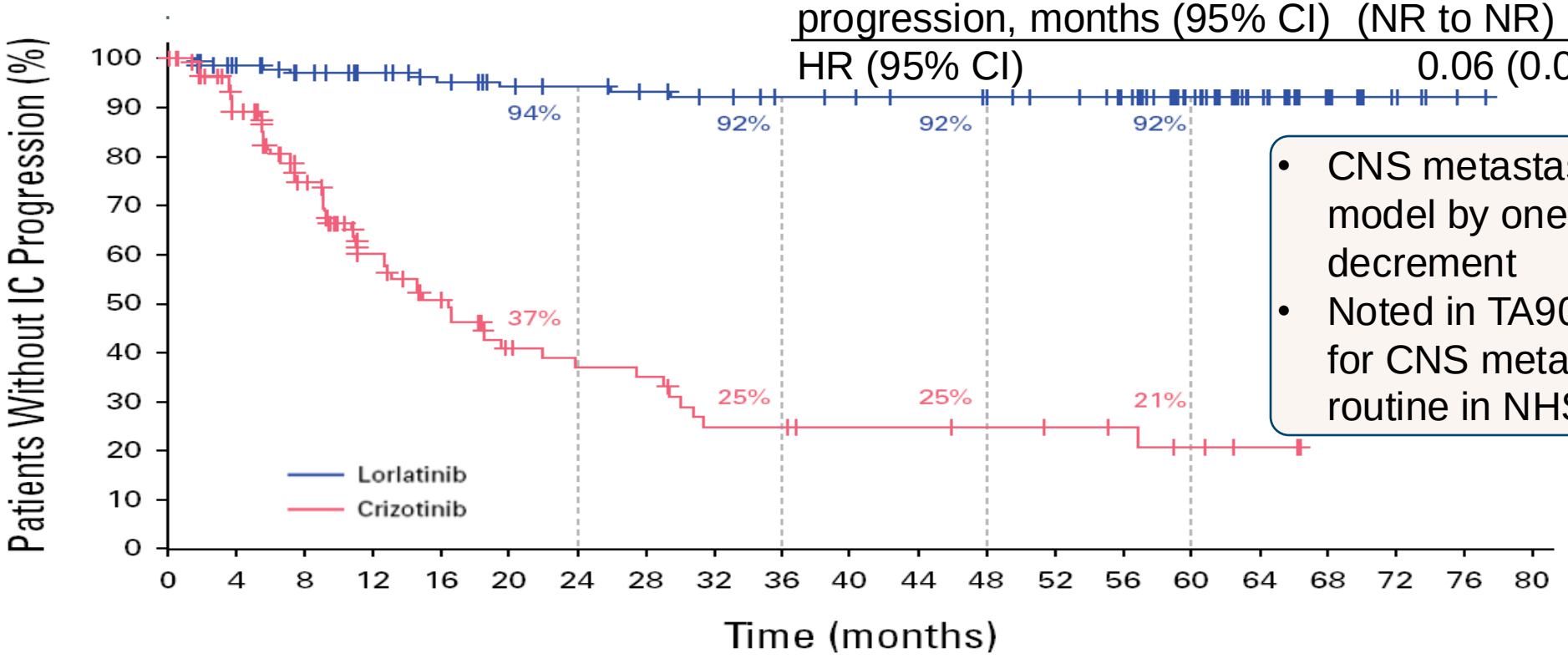
# CROWN secondary outcome: Time to intracranial progression

Statistically and clinically significant improvement in time to intracranial progression

**Time to intracranial progression – investigator assessment**

*October 2023 data cut*

| | Lorlatinib (n=149) | Crizotinib (n=147) |
|---|---|---|
| Events, n | 9 | 65 |
| Time to intracranial progression, months (95% CI) | NR (NR to NR) | 16.4 (12.7 to 21.9) |
| HR (95% CI) | 0.06 (0.03 to 0.12) | |




- CNS metastases reflected in model by one-off cost + utility decrement
- Noted in TA909 – screening for CNS metastases not routine in NHS

CI, confidence interval; CNS, central nervous system; HR, hazard ratio; IC, intracranial; NR, not reported.

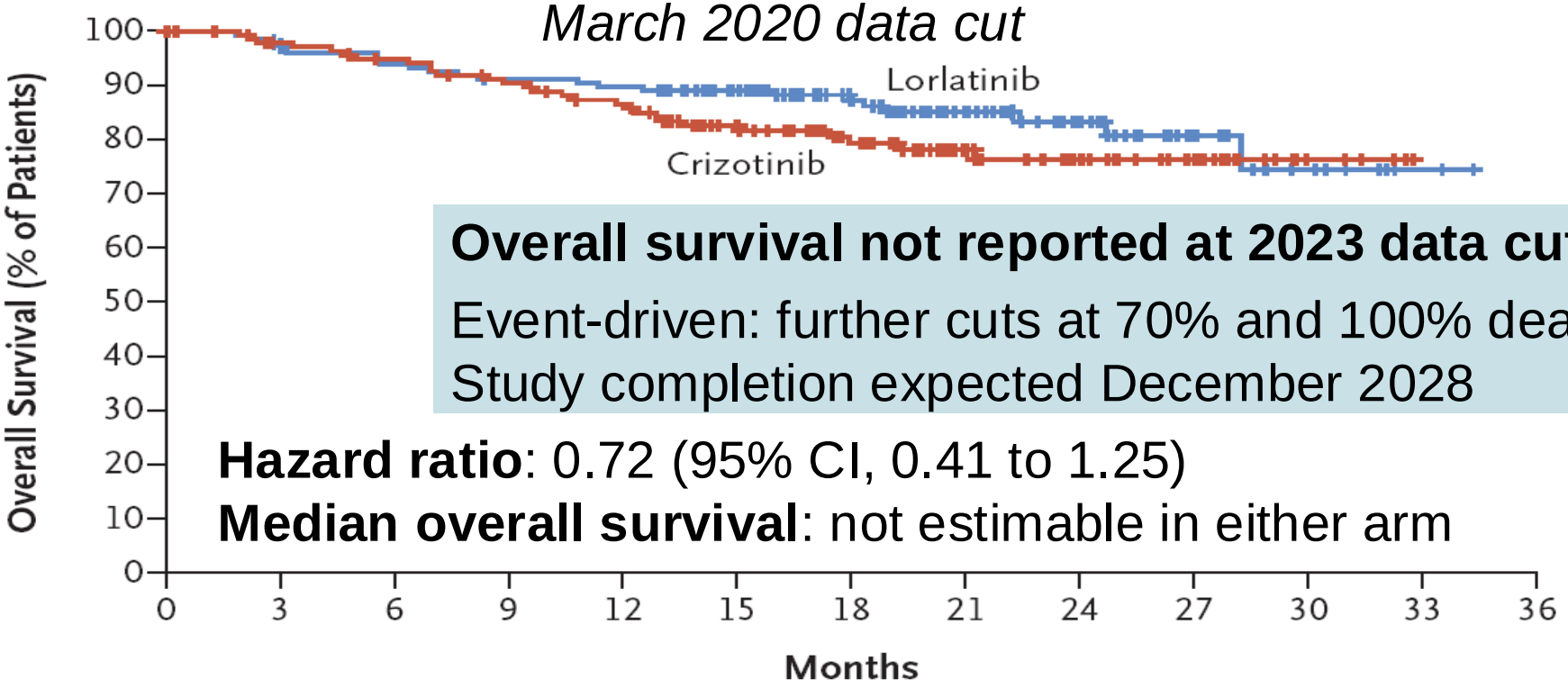
# CROWN secondary outcome: Overall survival

**Presented in TA909 – Mar 20 data cut**

Overall survival data immature – no new data but further data cuts in future

**Overall survival**

*March 2020 data cut*




**Overall survival not reported at 2023 data cut**

Event-driven: further cuts at 70% and 100% deaths

Study completion expected December 2028

**Hazard ratio**: 0.72 (95% CI, 0.41 to 1.25)

**Median overall survival**: not estimable in either arm

| No. at Risk | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lorlatinib | 149 | 148 | 141 | 138 | 135 | 133 | 131 | 122 | 101 | 85 | 63 | 50 | 38 | 27 | 13 | 8 | 4 | 1 | 0 |
| Crizotinib | 147 | 139 | 133 | 127 | 122 | 116 | 111 | 97 | 85 | 68 | 55 | 40 | 31 | 22 | 12 | 5 | 3 | 0 | 0 |

CI, confidence interval.

# Other clinical data company uses in its model

| | Study 1001 | PROFILE 1001/1005 |
|---|---|---|
| **Design** | Single arm, open label, phase 1/2 | Pooled retrospective analysis of 2 single arm, open label, phase 1 and 2 trials |
| **Population** | • EXP1 cohort: n=30 treatment-naïve<br>• EXP3B to 5 cohort: n=139 progression after ≥1 TKIs | • ALK+ NSCLC with progression |
| **Relevant intervention** | • EXP1: lorlatinib<br>• EXP3B to 5: lorlatinib after previous TKI | Chemotherapy following progression on crizotinib |
| **Comparator** | None | None |
| **Used in model?** | EXP1: long-term survival for lorlatinib<br>EXP3B to 5: Post-progression survival for comparators | Post-progression survival for chemotherapy after lorlatinib or comparators |
| **Median follow-up** | 72.7 months | Not reported |
| **Locations** | Multinational (0 UK sites) | US (1001), Multinational (1005; 8 UK sites) |

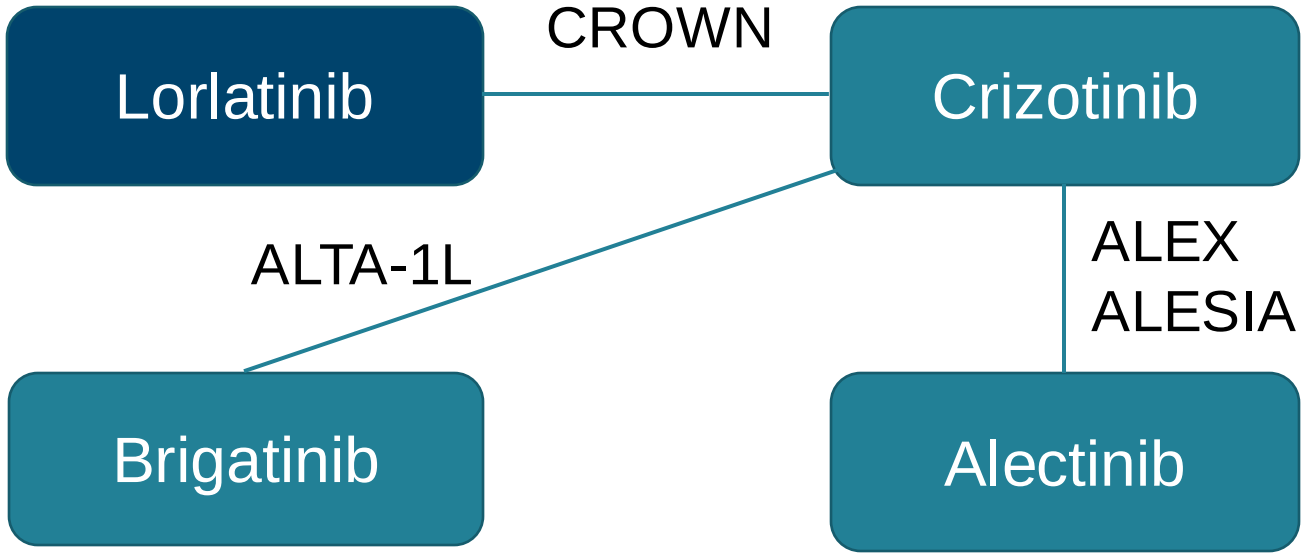
NICE ALK, Anaplastic lymphoma kinase; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

# Network meta-analysis

No head-to-head trials of lorlatinib and alectinib/brigatinib

**Company approach**

- Standard Bayesian network meta-analysis
- Fixed effects model used for all analyses




**Results** – hazard ratio (95% CrI) lorlatinib versus

| | Progression-free survival | | Intracranial progression | Overall survival | |
|---|---|---|---|---|---|
| | Independent | Investigator | Investigator | Unadjusted | Crossover adj. |
| Alectinib | 0.59 (0.37, 0.95) | 0.49 (0.32, 0.75) | 0.39 (0.17, 0.89) | 1.12 (0.59, 2.11) | 1.20 (0.57, 2.52) |
| Brigatinib | 0.56 (0.34, 0.93) | 0.44 (0.27, 0.72) | 0.20 (0.07, 0.54) | 0.89 (0.44, 1.78) | 1.44 (0.65, 3.18) |

adj., adjusted; CrI, credible interval.

Hazard ratio less than 1 = favours lorlatinib

# Key issue: Generalising treatment sequences from trial to NHS

NHS treatment sequencing not reflected in intervention or comparator trials

## CROWN

**Lorlatinib** versus **Crizotinib**

Progression → 2nd line TKI

- 7% lorlatinib
- 44% other

Progression → 2nd line TKI

- 4% lorlatinib
- 88% other

## ALEX

**Alectinib** versus **Crizotinib**

Progression → 2nd+ line TKI

- 13% lorlatinib
- 33% other

Progression → 2nd+ line TKI

- 9% lorlatinib
- 60% other

## ALTA-1L

**Brigatinib** versus **Crizotinib**

Progression → 2nd+ line TKI

- 30% lorlatinib
- 45% other

Progression → 2nd+ line TKI

- 21% lorlatinib
- 118% other

## NHS practice

**Lorlatinib** versus **Alectinib** or **Brigatinib**

**Lorlatinib** (if limited progression) → Chemo/BSC

Chemo/BSC

**Lorlatinib** → Chemo/BSC

**People in trials:**

- Had 2nd line treatments <u>not</u> used in NHS
- Didn't have treatments that <u>are</u> used in NHS
- If NHS treatments were had, they were in different proportions

BSC, best supportive care; TKI, tyrosine kinase inhibitor.

# Key issue: Generalising treatment sequences from trial to NHS

NHS treatment sequencing not reflected in intervention or comparator trials

**Company:**

- Acknowledge CROWN + trials for comparators do not reflect NHS treatment
- To reduce uncertainty:
  - ↳ Base case state transition approach for comparators
  - ↳ Post-progression survival from Study 1001 EXP3B to 5 cohorts for 2nd line lorlatinib
  - ↳ Matching-adjusted indirect comparison to compare to lorlatinib to alectinib using real-world data
    - ↳ When adjusted to CROWN baseline characteristics, real-world outcomes for alectinib similar to those observed in ALEX and ALESIA trials (see appendix)

**EAG:**

- Company efforts have limitations – data not randomised
- Study 1001 + PROFILE 1001/1005 do not represent NHS practice
- Real-world MAIC has limitations, any comparison with lorlatinib – unanchored

NICE MAIC, matching-adjusted indirect comparison; TKI, tyrosine kinase inhibitor.

# Key issue: Immature overall survival data from CROWN

No new data – uncertainty in overall survival unchanged

**Background:** OS not measured at October 2023 cut, protocol requires 139 (70%) deaths

**Company:**

- Acknowledge long-term OS is uncertain
- Clinical advice – expect PFS will translate to OS, with potential 10-year median
- Study 1001 (EXP1 cohort, n=30, follow-up to 73 months) pooled with CROWN to inform long-term OS extrapolations

**EAG:**

- OS data remains very immature – median not estimable in either treatment arm
- Company have provided no evidence to justify PFS-OS relationship in the model
- Value of Study 1001 is limited due to size, design, dissimilarity with CROWN
- Further CROWN cuts of limited value due to issues in 2$^{nd}$ line treatments including getting lorlatinib 2$^{nd}$ line instead of 1$^{st}$ line

NICE OS, overall survival; PFS, progression-free survival.

# Key issue: Indirect treatment comparison for overall survival

Benefit for overall survival highly uncertain

**Company**

- Network meta-analysis – no difference in overall survival between lorlatinib + comparators
- CROWN results are uncertain, but hazard ratio should improve with further cuts

**EAG**

- CROWN overall survival data very immature so uncertain
- Proportional hazards assumption likely violated
  - Approaches to resolve this would generate more uncertainty
- High risk of confounding due to crossover + treatment sequences that do not reflect NHS
- Can make no conclusions whether people on lorlatinib live longer, same, or shorter than current NHS 1st line treatments

- What does the network meta-analysis show for lorlatinib compared with alectinib/brigatinib? Are the results valid?
- Would it be better to use randomised evidence or evidence from external sources to model overall survival? Would more data on overall survival help?



NMA, network meta-analysis; OS, overall survival

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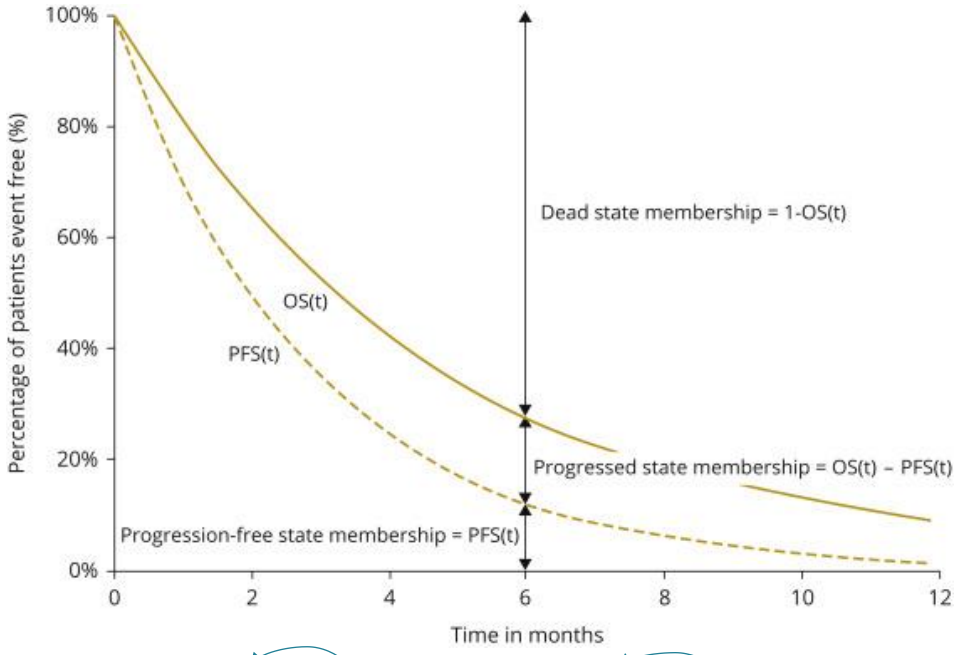
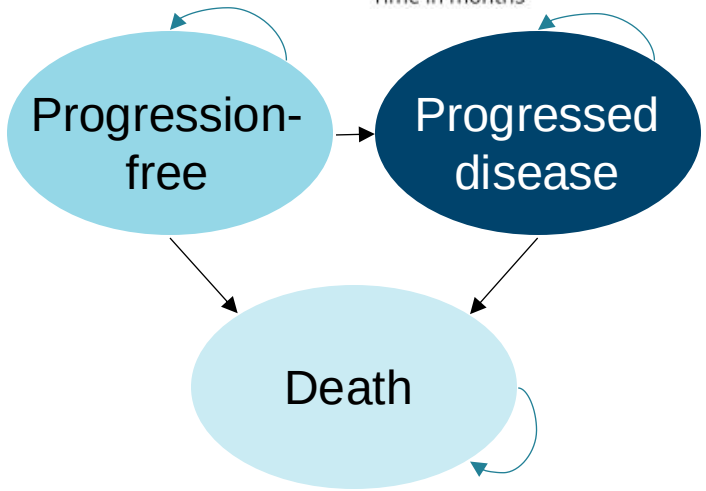
# Company's model overview

## Three state model structure




Lorlatinib affects **costs** by:

- ↑ 1st line treatment costs
- ↓ 2nd line treatment costs

Lorlatinib affects **QALYs** by:

- ↑ quality of life when progression free
- ↑ progression-free survival
- ↑ overall survival

**Assumptions that drive ICER:**

- Model structure
- ↑ progression-free survival benefit
- How time on treatment is modelled
- How the PAS is applied to lorlatinib in comparator arm

NICE

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; PAS, Patient Access Scheme.

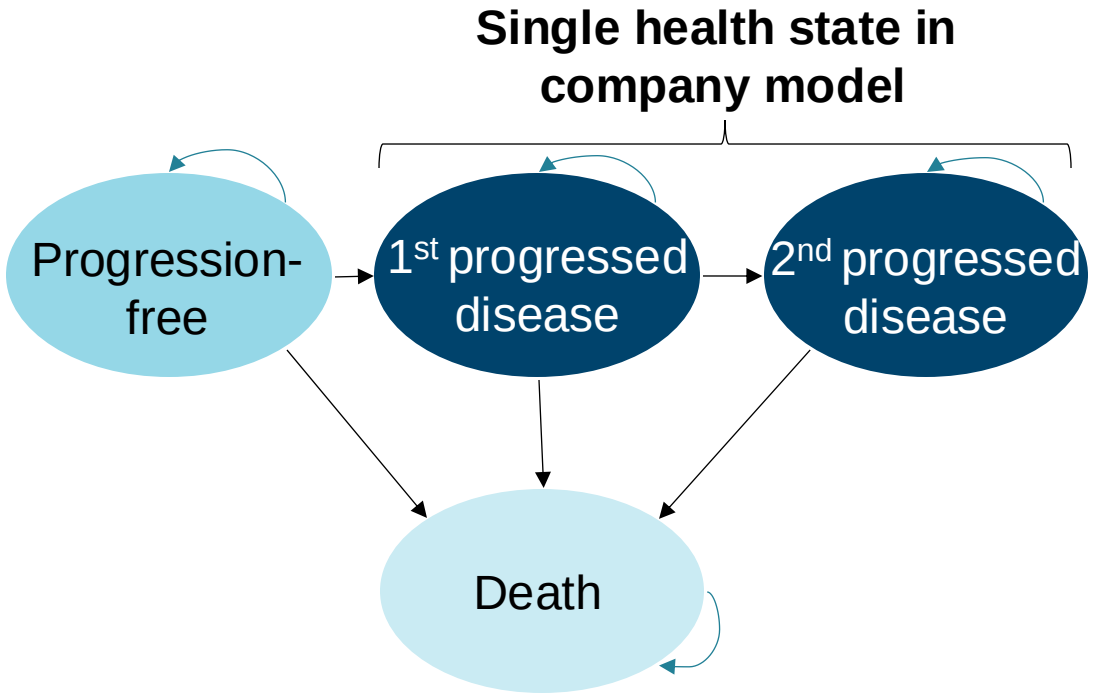
# Key issue: Treatment sequences in trials do not reflect NHS

EAG propose a 4-state model to better reflect 2nd line treatments

**EAG:**

- Company model unable to fully account for the impact of 2nd line treatments within catch-all progressed disease health state
- Propose 4 state model to better capture 2nd line by splitting progressed state into 1st + 2nd progression (not implemented due to time)
- Proposed benefits:
  - Differentiate cost & benefits of lorlatinib 2nd line compared to alternatives
  - Better estimate costs in PD state – currently ToT is independent of time in PD – time spent in PD greatly impacts model predictions
  - Transparency on where the health benefits are accrued and inform extrapolations in PD

**EAG suggested 4-state model**




PD, progressed disease; ToT, time on treatment.

NMA, network meta-analysis;
PFS, progression-free survival.

# Key issue: Inconsistent model structure

Company model uses different modelling approaches for lorlatinib + comparators

**Company:** Trials of comparators did not use lorlatinib 2nd line – may underestimate efficacy

- To better reflect NHS, used data from additional, external sources
- This approach required state transition model for comparator post-progression survival
- Different to partitioned survival model used for lorlatinib and comparator PFS

**EAG:** Should use consistent modelling approach for intervention and comparators

- Fundamentally different assumptions for different models, will lead to bias in results
- Prefer state transition due to generalisability issues with CROWN + issues with using NMA for overall survival – better to use external source

| | Partitioned survival model | State transition model |
|---|---|---|
| *Pros* | Comparisons based on randomised evidence | • Emphasises mature CROWN PFS – not confounded by 2nd line treatments<br>• Can incorporate real-world data |
| *Cons* | • Overall survival immature and confounded by 2nd line treatments<br>• Implausible results for comparators | • Modelled overall survival no longer based on randomised comparisons<br>• Limited evidence for post-progression survival |

# Key issue: Inconsistent model structure

EAG: state transition should be used for both lorlatinib and comparator PPS

| | Company base case | | EAG base case | |
|---|---|---|---|---|
| | **Lorlatinib** | **Alectinib/brigatinib** | **Lorlatinib** | **Alectinib/brigatinib** |
| **Progression-free survival** | Fitted curves to lorlatinib PFS<br>*Source*: CROWN | Fitted curves to *crizotinib* PFS + hazard ratio<br>*Source*: CROWN + NMA | Same as company | Fitted curves to *lorlatinib* PFS + hazard ratio<br>*Source*: CROWN + NMA |
| **Post-progression survival** | OS minus PFS | Transition probability estimated (STM)<br>*Source*: Study 1001 (EXP3B-5) and PROFILE 1001/1005 | Transition probability estimated (STM)<br>*Source*: PROFILE 1001/1005 | Same as company |
| **Overall survival** | Fitted curves to lorlatinib OS<br>*Source*: pooled CROWN + Study 1001 (EXP1) | PFS plus PPS | PFS plus PPS | Same as company |

NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; STM, state transition model.

# Model structure key questions

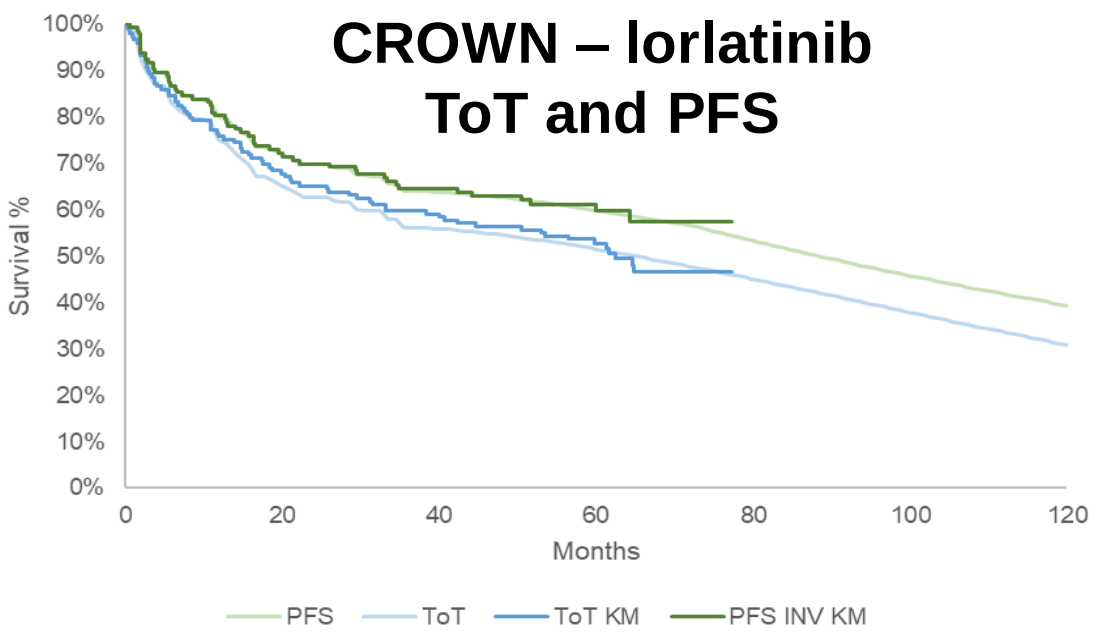
- How could modelling better reflect treatment options at 2nd line and beyond?
- What is committee's preferred approach for modelling post-progression and overall survival for lorlatinib (state transition vs. partitioned survival model)?

# Key issue: lorlatinib time on treatment and treatment beyond progression

Company uses time on treatment; EAG uses PFS + treatment beyond progression

**Company:** CROWN time on treatment data most robust

- Higher chance of stopping lorlatinib before progression due to long duration
- CROWN permitted treatment beyond progression, but not included in model because clinicians chose not to




**EAG:** TA909 – committee concluded treatment beyond progression should be included and company updated base accepted this

- Comparators in model assume ToT = PFS
- Clinical advice: NHS treatment duration longer than CROWN + often beyond progression
- Use lorlatinib ToT = PFS and treatment beyond progression (5.7 months for 75.6%) to model costs, not benefits due to lack of data

How should lorlatinib time on treatment and treatment beyond progression be modelled?

PFS, progression-free survival; ToT, time on treatment.

INV, investigator; PFS, progression-free survival.

# Key issue: Extrapolating investigator PFS

New 5-year data; Company and EAG differ on reference arm and survival curve choice

**Company:**

- Fit independent curves to lorlatinib and crizotinib from CROWN (fit statistics)
- Hazard ratio from NMA applied to crizotinib for alectinib and brigatinib
- **Lorlatinib**: 36-month piecewise Weibull
- **Crizotinib**: Weibull full extrapolation

**EAG:**

- Inconsistent to use piecewise for lorlatinib + fully extrapolated for comparators, and survival is implausible without waning (also see appendix)
- Prefer to use lorlatinib as reference arm + apply 36-month piecewise Gompertz to extrapolate

Which is the most appropriate method for PFS extrapolation?

[redacted]

| PFS % | Company | EAG |
|---|---|---|
| 1 year | 80.2% | 80.2% |
| 5 years | 60.5% | 60.5% |
| 10 years | 40.9% | 27.9% |
| 20 years | 10.6% | 0.0% |
| 30 years | 1.6% | 0.0% |

# Key issue: Relative treatment effect waning

EAG: waning should not be used to correct implausible extrapolations

**Company:**

- PFS uncertain after 10 years – as in TA909, hazards waned to crizotinib

**EAG:** Waning reasonable, but should be used to address durability of effect rather than correct implausible PFS

- In company base case, lorlatinib PFS estimations vary depending on crizotinib distribution (see appendix)
- EAG base case does not use crizotinib as reference arm, so at 10 years, hazards waned to alectinib

How should relative treatment effect waning be applied?

[redacted]

**Company PFS estimations with waning**

| | Lorlatinib | Alectinib | Brigatinib |
|---|---|---|---|
| 1 year | 80.2% | 74.7% | 72.4% |
| 5 years | 60.5% | 21.5% | 18.3% |
| 10 years | 40.9% | 4.2% | 3.0% |
| 15 years | 0.6% | 0.1% | 0% |
| 20 years | 0% | 0% | 0% |

NICE PFS, progression-free survival.

# Key issue: Utility values

See appendix for utility values

EAG disagree with treatment-specific utilities and suggest higher values after progression

**Company:** Apply treatment-specific and on/off treatment PFS utilities to capture specific experience of each treatment

- CROWN progressed disease utilities implausibly high – use brigatinib values
  - ↳ High progressed utility in CROWN as analysis based on small number of patients, collected close to progression

**EAG:** Company changed approach since TA909, where agreed to use brigatinib utilities

- Treatment-specific utilities contradict clinical advice, previous appraisals + inconsistent with PD state
  - ↳ Remove treatment-specific utilities
- In PFS, different on/off-treatment utilities potentially double-counts adverse event disutility
  - ↳ Remove PFS on/off treatment
- In progressed disease, using 2nd line ALK-inhibitors could mean higher utility
  - ↳ Add PD on/off treatment, with value about midpoint between PFS and PD off-treatment

Is it appropriate to reject CROWN utility? Which utility values are most appropriate?

ALK, Anaplastic lymphoma kinase; CNS, central nervous system; PD, progressed disease; PFS, progression-free survival.

# Key issue: Modelling lorlatinib conditional PAS

Company and EAG disagree on methodological approach for implementing PAS

**Background:** Lorlatinib has existing PAS for 2nd line use

- Lorlatinib offered with new PAS on condition of positive recommendation (would apply at 1st line and 2nd line if positive recommendation)

**Company:** Decision problem compares world with 1st line lorlatinib versus world without

- So, new PAS only available in intervention arm, does not exist in comparator arm

**EAG:** Company incorrectly frames decision as 'before and after'

- Means model results are invalidated with positive guidance, as new PAS applies to both arms – comparator becomes significantly cheaper
- New PAS should be used for both 1st and 2nd line lorlatinib in model

**NICE tech team advice:** question of interpretation and application of methods

- Limitations of both approaches
- Company approach reflects current decision for committee; EAG approach more appropriate for decision on optimal treatment pathway (e.g. in a guideline)

How should the conditional PAS be implemented?



PAS, patient access scheme

# Summary of company and EAG base case assumptions

| Assumption | Company base case | EAG base case |
|---|---|---|
| **Model structure for PPS** | • Lorlatinib: partitioned survival<br>• Comparators: state transition | • Lorlatinib: state transition<br>• Comparators: state transition |
| **Time on treatment** | CROWN time on treatment | CROWN progression-free survival |
| **Lorlatinib treatment beyond progression** | Not included | Included – 75.6% continue lorlatinib for 5.7 months |
| **Progression-free survival** | CROWN + survival analysis<br>• Lorlatinib: 36m piecewise Weibull<br>• Comparators: NMA hazard ratio applied to crizotinib<br>Reference arm: crizotinib | CROWN + survival analysis<br>• Lorlatinib: 36m piecewise Gompertz<br>• Comparators: NMA hazard ratio applied to lorlatinib<br>Reference arm: lorlatinib |
| **Post-progression survival** | • Lorlatinib: Sum of OS – PFS (PSM)<br>• Comparators: Study 1001 (EXP3B-5) | • Lorlatinib: PROFILE 1001/1005 (STM)<br>• Comparators: Study 1001 (EXP3B-5) |
| **Overall survival** | • Lorlatinib: pooled CROWN and Study 1001 (EXP1) + survival analysis<br>• Comparators: Sum of PFS + PPS | • Lorlatinib: Sum of PFS + PPS<br>• Comparators: Sum of PFS + PPS |
| **Waning** | Waning to crizotinib hazards from 10yrs | Waning to alectinib hazards from 10yrs |

NICE NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; PSM, partitioned survival model; STM, state transition model.

# Summary of company and EAG base case assumptions

| Assumption | Company base case | EAG base case |
|---|---|---|
| **Utility values** | • PFS: CROWN and past appraisals, treatment-specific, on/off treatment-specific<br>• PD: TA670 (brigatinib), no on/off treatment-specific | • PFS: TA670 (brigatinib), not treatment-specific, not on/off treatment-specific<br>• PD: TA670 (brigatinib), on/off treatment-specific |
| **Lorlatinib conditional PAS implementation** | Use of new PAS for 1st line and existing PAS for 2nd line (comparator arm) | Use of new PAS for 1st line and 2nd line |

NICE PAS, patient access scheme; PD, progressed disease; PFS, progression-free survival.

# Results – cost-effectiveness ranges

**Confidential discounts for comparators – ICERs in Part 2 slides**
**ICER ranges presented below**

## Summary – lorlatinib versus alectinib/brigatinib for untreated ALK+ advanced NSCLC*

Company base case probabilistic ICER:
- < £20,000 per QALY gained

EAG base case probabilistic ICER:
- > £30,000 per QALY gained

Company and EAG scenario analyses:
- Lowest ICER: < £20,000 per QALY gained
- Highest ICER: > £30,000 per QALY gained

*Both company and EAG agree a severity weighting does not apply
ALK, anaplastic lymphoma kinase; ICER, incremental cost-effectiveness ratio; NSCLC, non-small cell lung cancer; QALY, quality-adjusted life year.

# Committee decision making slide

| Assumption | Question for committee |
|---|---|
| **Comparators** | What is(are) the most appropriate comparator(s) for lorlatinib? |
| **Marketing authorisation** | When would people stop taking lorlatinib in the NHS? |
| **Immature clinical data and NMA** | • What does the network meta-analysis show for lorlatinib compared with alectinib/brigatinib? Are the results valid?<br>• Would it be better to use randomised evidence or evidence from external sources to model overall survival? Would more data on overall survival help? |
| **Model structure** | • How could modelling better reflect treatment options at 2nd line and beyond?<br>• What is committee's preferred approach for modelling post-progression and overall survival for lorlatinib (state transition vs. partitioned survival model)? |
| **Time on treatment** | How should lorlatinib time on treatment and treatment beyond progression be modelled? |
| **PFS extrapolation** | Which is the most appropriate method for PFS extrapolation? |

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NMA, network meta-analysis; PFS, progression-free survival; PSM, partitioned survival model; STM, state transition model.

# Committee decision making slide

| Assumption | Question for committee |
|---|---|
| **Waning** | How should relative treatment effect waning be applied? |
| **Utilities** | Is it appropriate to reject CROWN utility? Which utility values are most appropriate? |
| **PAS** | How should the conditional PAS be implemented? |
| **Other factors** | • Are there any equality considerations that need to be accounted for?<br>• Are there any benefits of lorlatinib that are not captured in the QALY calculations?<br>• Is there any uncertainty in the modelling that needs to be accounted for? |
| **ICER threshold** | What is the committee's preferred ICER threshold? |
| **Preferred ICER** | What is the committee's preferred ICER? |
| **Managed access** | • Is the committee's preferred ICER below the threshold?<br>• If no, could key uncertainties be sufficiently resolved during a period of managed access? (see next slide) |

NICE ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; QALY, quality-adjusted life year.

# 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**

# Thank you

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# Supplementary appendix

NICE National Institute for Health and Care Excellence

# Patient perspectives

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PFS improvement with lorlatinib very important for patients

**Submissions from ALK Positive UK and Roy Castle Lung Foundation**

ALK rearrangement more likely to be never smokers and younger than the general lung cancer population

Symptoms are distressing for patients, who often have young families and are responsible for raising children

Lorlatinib data seem promising due to PFS gain and effect on brain metastases

Effective management of brain metastases is vital for a good QoL for people and the chance to be stable for as long as possible

Need for additional more effective treatments in this patient group

‘Increase in PFS with Lorlatinib is seen as a game-changer’

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ALK, Anaplastic lymphoma kinase; PFS, progression-free survival; QoL, quality of life; TKI, tyrosine kinase inhibitor

# Clinical perspectives

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Lorlatinib has impressive PFS results and manageable toxicities

**Submission from British Thoracic Oncology Group**

Main aim of treatment is to prolong survival

Clinically significant response:

- Reduction in tumour size
- Disease control

Control of CNS disease remains a key outcome for clinicians and patients

Different side effects with lorlatinib but not more difficult to manage

‘PFS benefit is one of the most pronounced and impressive data seen in solid tumours’

‘Lorlatinib has a well-established toxicity profile with effective guidance on management’

CNS, central nervous system; PFS, progression-free survival; QoL, quality of life.

# Treatments after progression in CROWN and comparator trials

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**Company:**

- Higher 2nd line ALK inhibitor use in ALESIA and ALTA-1L compared to CROWN, similar use in ALEX

| | | | Treatments after progression | | | | |
|---|---|---|---|---|---|---|---|
| Study | Treatment | N | Lorlatinib | Alectinib | Brigatinib | Crizotinib | Ceritinib |
| CROWN | Lorlatinib | 149 | 3/46 (6.5%) | 12/46 (26.1%) | 1/46 (2.2%) | 4/46 (8.7%) | 3/46 (6.5%) |
| | Crizotinib | 147 | 4/110 (3.6%) | 68/110 (61.8%) | 21/110 (19.1%) | 5/110 (4.5%) | 3/110 (2.7%) |
| ALEX | Alectinib | 152 | 11/84 (13.1%) | 2/84 (2.4%) | 8/84 (9.5%) | 11/84 (13.1%) | 7/84 (8.3%) |
| | Crizotinib | 151 | 10/114 (8.8%) | 24/114 (21.1%) | 11/114 (9.6%) | 9/114 (7.9%) | 24/114 (21.1%) |
| ALESIA | Alectinib | 125 | 3/20 (15.0%) | 1/20 (5.0%) | 0/20 (0%) | 4/20 (20%) | 0/20 (0%) |
| | Crizotinib | 62 | 1/30 (3.3%) | 4/30 (13.3%) | 4/30 (13.3%) | 1/30 (3.3%) | 2/30 (6.7%) |
| ALTA-1L | Brigatinib | 137 | 22/74 (29.7%) | 16/74 (21.6%) | 2/74 (2.7%) | 11/74 (14.9%) | 4/74 (5.4%) |
| | Crizotinib | 138 | 21/101 (20.8%) | 28/101 (27.7%) | 80/101 (79.2%) | 6/101 (5.9%) | 5/101 (5.0%) |

# Flatiron real-world database alectinib results

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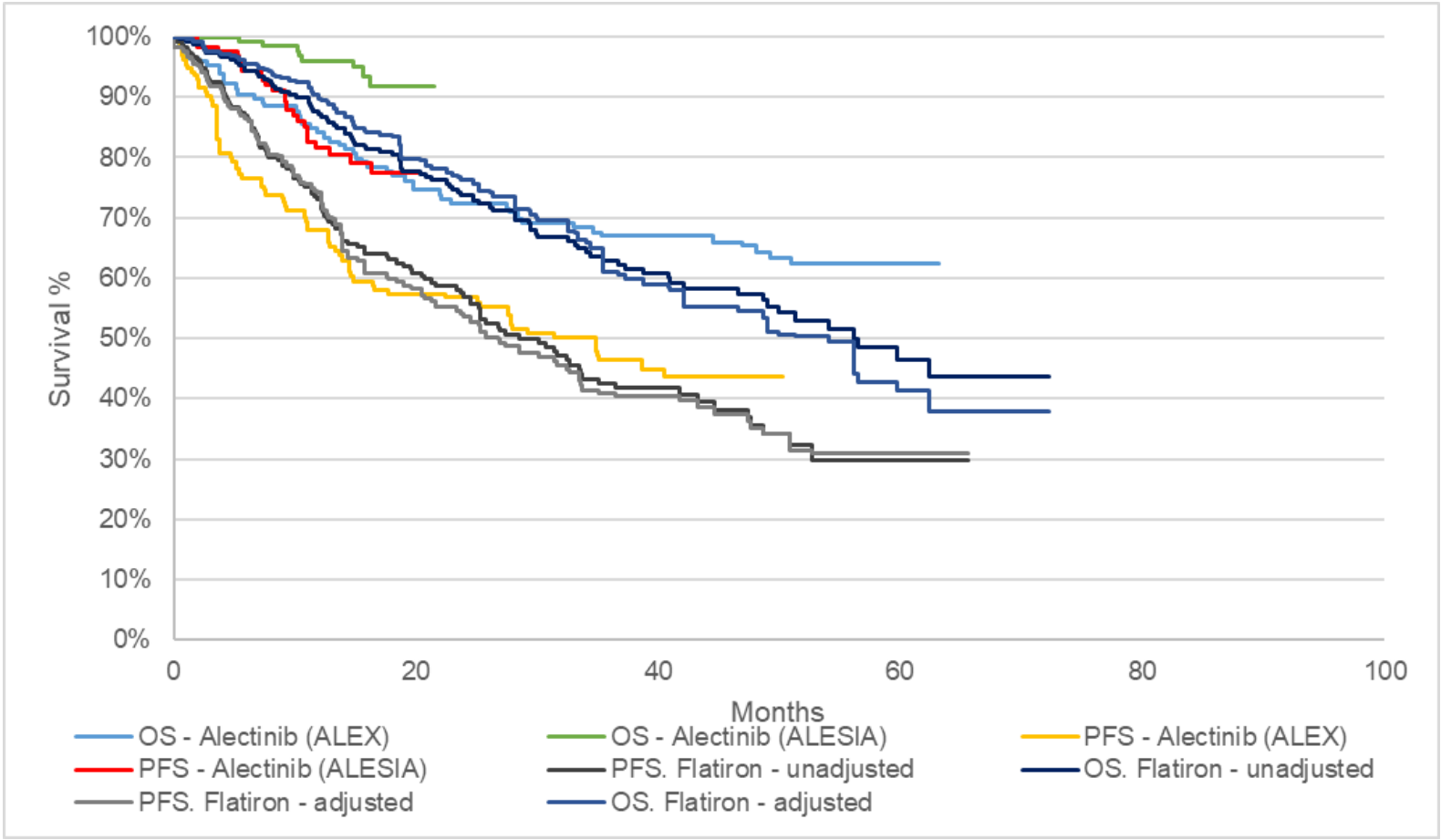
**Company:**

- Flatiron database contained people who had alectinib 1st line
- 2nd line treatments more reflective of NHS: ~2/3rds lorlatinib
- Population adjustment performed to match Flatiron population to CROWN
- Similar PFS/OS outcomes between Flatiron population and ALEX/ALESIA




NICE OS, overall survival; PFS, progression-free survival.

# PFS survival curve fit statistics

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**INV assessed PFS extrapolation – lorlatinib 36 months piecewise**

| Distribution | AIC | AIC rank | BIC | BIC rank |
|---|---|---|---|---|
| **Exponential** | 83.86 | 1 | 86.26 | 1 |
| **Gen. gamma** | 84.78 | 5 | 89.57 | 5 |
| **Gompertz** | 85.61 | 7 | 92.79 | 7 |
| **Log-logistic** | 84.72 | 3 | 89.51 | 3 |
| **Log-normal** | 84.74 | 4 | 89.53 | 4 |
| **Weibull** | 84.42 | 2 | 89.21 | 2 |
| **Gamma** | 85.31 | 6 | 90.10 | 6 |

**INV assessed PFS extrapolation – crizotinib**

| Distribution | AIC | AIC rank | BIC | BIC rank |
|---|---|---|---|---|
| **Exponential** | 862.19 | 6 | 865.18 | 5 |
| **Gen. gamma** | 829.27 | 2 | 838.24 | 3 |
| **Gompertz** | 855.00 | 4 | 860.98 | 4 |
| **Log-logistic** | 825.80 | 1 | 831.78 | 1 |
| **Log-normal** | 830.74 | 3 | 836.72 | 2 |
| **Weibull** | 863.98 | 7 | 869.96 | 7 |
| **Gamma** | 860.96 | 5 | 866.94 | 6 |

AIC, Akaike information criterion; BIC, Bayesian information criterion; INV, investigator; PFS, progression-free survival.

# Lorlatinib PFS landmark estimations without waning

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| Distribution | Lorlatinib PFS landmarks (36 months piecewise) | | | | | |
|---|---|---|---|---|---|---|
| | 1 year | 5 years | 10 years | 15 years | 20 years | 30 years |
| **Exponential** | 80.2% | 60.2% | 50.4% | 42.2% | 35.3% | 24.7% |
| **Gen. gamma** | 80.2% | 59.3% | 54.8% | 53.0% | 51.9% | 50.5% |
| **Gompertz**<br>EAG base case | 80.2% | 60.5% | 27.9% | 0.1% | 0.0% | 0.0% |
| **Log-logistic** | 80.2% | 60.5% | 43.0% | 29.6% | 21.2% | 12.3% |
| **Log-normal** | 80.2% | 60.4% | 47.1% | 38.0% | 31.6% | 23.3% |
| **Weibull**<br>Company base case | 80.2% | 60.5% | 40.9% | 22.5% | 10.6% | 1.6% |
| **Gamma** | 80.2% | 60.5% | 42.2% | 26.4% | 15.7% | 5.1% |

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PFS, progression-free survival.

# Lorlatinib PFS landmarks with different crizotinib extrapolations

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- In company base case, at 10 years, lorlatinib PFS hazard waned to crizotinib
- So, crizotinib distribution affects lorlatinib modelled PFS after 10 years

| Crizotinib distribution | Lorlatinib PFS landmarks | | | |
|---|---|---|---|---|
| | 10 years | 15 years | 20 years | 30 years |
| **No waning** | 40.9% | 22.5% | 10.6% | 1.6% |
| **Exponential** | 40.9% | 0.9% | 0.0% | 0.0% |
| **Generalised gamma** | 40.9% | 18.6% | 10.4% | 4.4% |
| **Gompertz** | 40.9% | 33.3% | 31.6% | 31.0% |
| **Log-logistic** | 40.9% | 19.4% | 11.3% | 5.3% |
| **Log-normal** | 40.9% | 11.3% | 4.1% | 0.8% |
| **Weibull** – company base case | 40.9% | 0.6% | 0.0% | 0.0% |
| **Gamma** | 40.9% | 0.4% | 0.0% | 0.0% |

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PFS, progression-free survival.

# Utility values

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| Health state | Treatment | TA909 value | Company value | EAG value |
|---|---|---|---|---|
| Progression-free (on treatment) | Lorlatinib | 0.793 | 0.845 | 0.793 |
| | Brigatinib | 0.793 | 0.793 | 0.793 |
| | Alectinib | 0.793 | 0.814 | 0.793 |
| Progression-free (off treatment) | Lorlatinib | 0.793 | 0.768 | 0.793 |
| | Brigatinib | 0.793 | 0.793 | 0.793 |
| | Alectinib | 0.793 | 0.814 | 0.793 |
| Progressed (on treatment) | Lorlatinib | 0.624 | 0.624 | 0.725 |
| | Brigatinib | 0.624 | 0.624 | 0.725 |
| | Alectinib | 0.624 | 0.624 | 0.725 |
| Progressed (off treatment) | Lorlatinib | 0.624 | 0.624 | 0.624 |
| | Brigatinib | 0.624 | 0.624 | 0.624 |
| | Alectinib | 0.624 | 0.624 | 0.624 |
| One-off utility for CNS progression (24 months duration) | Lorlatinib | N/A | 0.416 | 0.391 |
| | Brigatinib | N/A | 0.401 | 0.391 |
| | Alectinib | N/A | 0.391 | 0.391 |

CNS, central nervous system.

= change from company

# QALY weightings for severity

**Background**

- Expected total QALYs for the general population based on the ONS 2019-20 National life tables for England and Wales
- Population EQ-5D-3L data adjusted by age and sex derived from the Health Survey from England (HSE) 2014

| | QALYs of people without condition | QALYs with the condition on current treatment | Absolute QALY shortfall (has to be >12) | Proportional QALY shortfall (has to be >0.85) |
|---|---|---|---|---|
| **Company base case** | | | | |
| Alectinib | 13.58 | [redacted] | [redacted] | [redacted] |
| Brigatinib | 13.58 | [redacted] | [redacted] | [redacted] |
| **EAG base case** | | | | |
| Alectinib | 13.58 | [redacted] | [redacted] | [redacted] |
| Brigatinib | 13.58 | [redacted] | [redacted] | [redacted] |

**Both company and EAG agree that a QALY weighting does not apply**

ONS, Office for National Statistics; QALY, quality-adjusted life year.