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

PART 1
For screen – confidential information redacted

2nd meeting of Technology appraisal committee D [9 July 2025]

Chair: Megan John

External assessment group: CRD and CHE Technology Assessment Group, York

Technical team: Tom Palmer, Alex Sampson, Lorna Dunning

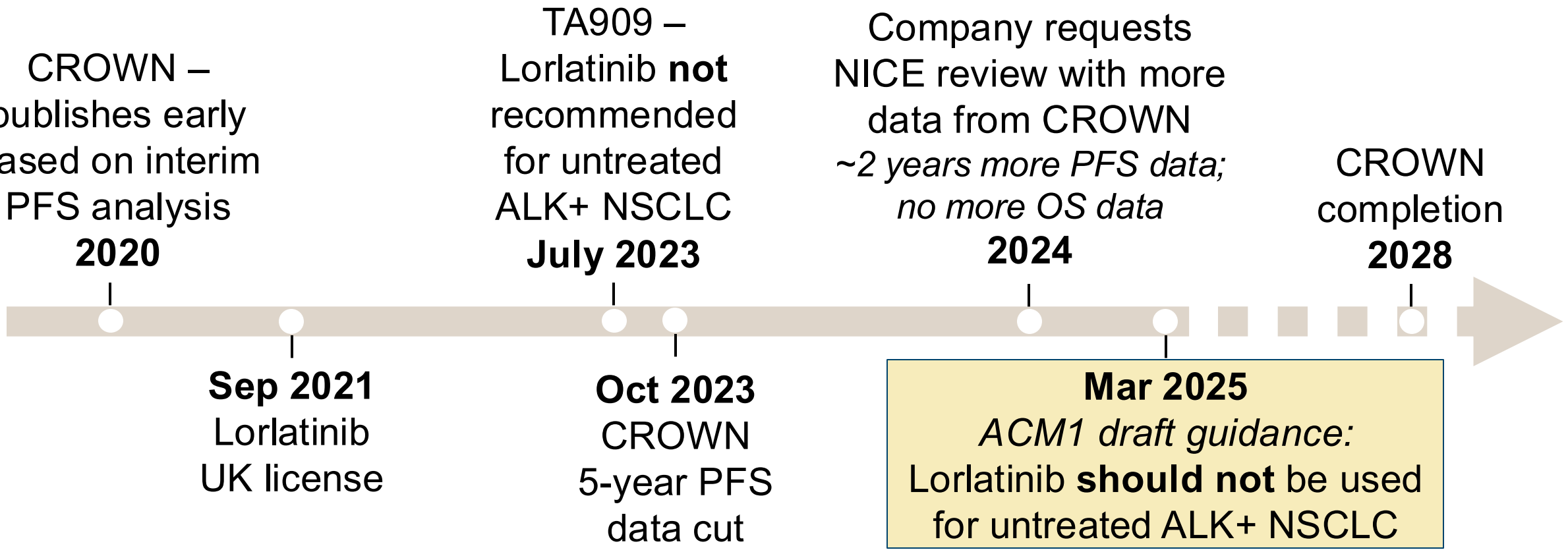
Company: Pfizer

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

- ✓ **Background and recap of appraisal committee meeting 1**
- ❑ Response to consultation

NICE National Institute for Health and Care Excellence

Lorlatinib timeline



NICE approved lorlatinib 2nd line

- TA628 (2020) – ALK+ NSCLC

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

Background + technology (lorlatinib, Lorviqua®, Pfizer)

Epidemiology, classification, causes

- In 2024, ≈ 39,097 people diagnosed with NSCLC in England & Wales
- 3 to 7% are ALK-positive

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

Marketing authorisation	Adults with ALK+ advanced NSCLC, not previously treated with an ALK inhibitor or following progression on an ALK inhibitor
Other NICE guidance	TA628 – following progression on an ALK inhibitor (2nd line)
Mechanism	Inhibits ALK + ROS1 receptor tyrosine kinases, acts against ALK resistance
Duration	'..as long as patient is deriving clinical benefit without unacceptable toxicity.'
Administration	100 mg orally once daily
Price	• List price: £5,283 per 30 x 100 mg tablets; £7,044 per 120 x 25 mg tablets • Patient access scheme is available

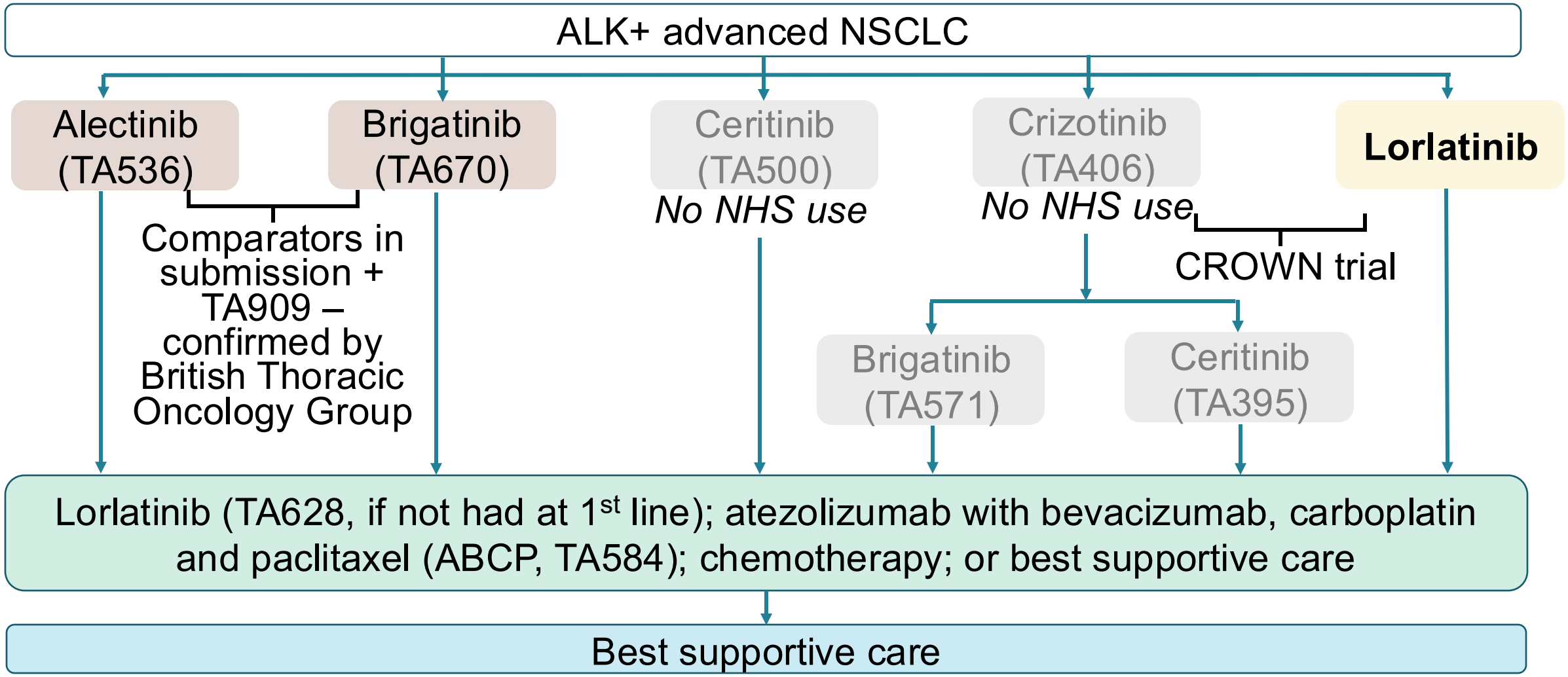
NICE

When would people stop taking lorlatinib in the NHS?

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

Treatment pathway

Loratinib licensed for 1st line (this appraisal), or 2nd line after alectinib or brigatinib (TA628)
No direct trial evidence of lorlatinib versus alectinib or brigatinib



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

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

- ❑ Background and recap of appraisal committee meeting 1
- ✓ **Response to consultation**

NICE National Institute for Health and Care Excellence

Summary of consultation responses received (1/2)

ALK Positive UK (patient)
- CROWN results widely described as ‘best-ever’ for a TKI
- Real-world data showing longer PFS with lorlatinib than alectinib
- Lorlatinib now available in Scotland, inequality of access across UK

Roy Castle Lung Cancer Foundation (patient)
- Lorlatinib access highly important to patients, particularly those with CNS metastases

British Thoracic Oncology Group (professional)
- Lack of new OS should be viewed as positive as pre-specified deaths not yet reached
- PFS benefit of lorlatinib likely to translate into OS benefit
- Concerned committee did not fully consider CNS metastases benefit of lorlatinib

Takeda (comparator; brigatinib)
- Minor comments to clarify that brigatinib is available as 2nd line treatment after crizotinib, but acknowledge this rarely happens in practice

 CNS, central nervous system; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Summary of consultation responses received (2/2)

Pfizer (company)

- Accept all committee preferred assumptions (see appendix)
- Consider some of the assumptions conservative (see appendix)
- As requested, use 4 health state model to better differentiate 2nd line treatment benefit
- Consider major uncertainties resolved, think higher threshold could be applied

Committee's key uncertainties at ACM1:		Company response to consultation:
Treatment sequences in trials don't reflect NHS	→	New model uses external sources to better reflect NHS sequences
CROWN OS immature, no new data since TA909	→	New model uses external sources to avoid using CROWN OS
OS NMA uncertainty due to above issues	→	OS NMA no longer used in model
3-state model can't differentiate 2nd line treatment	→	4-state model implemented
Non-randomised external sources used to model post-progression survival	→	Best available evidence used to inform new model, including non-randomised sources
Treatment after progression added to cost of each treatment but not to efficacy	→	Applied committee preferences

NMA, network meta-analysis; OS, overall survival

Key issues identified by the EAG for ACM2

Issues	ICER impact
New issues arising from 4-state model structure:	
Extrapolation of time to second progression	Low
Health state utility value for new progressed disease 2 state	Medium
Issues discussed at ACM1, for further consideration:	
Treatment beyond progression assumptions	Low
Proportion of people initiating 2nd line lorlatinib	High
Implementing patient access scheme discount for lorlatinib	Medium
Acceptable ICER	For deliberation

Equality

- No new equality issues raised at consultation

NICE ICER, incremental cost-effectiveness ratio.

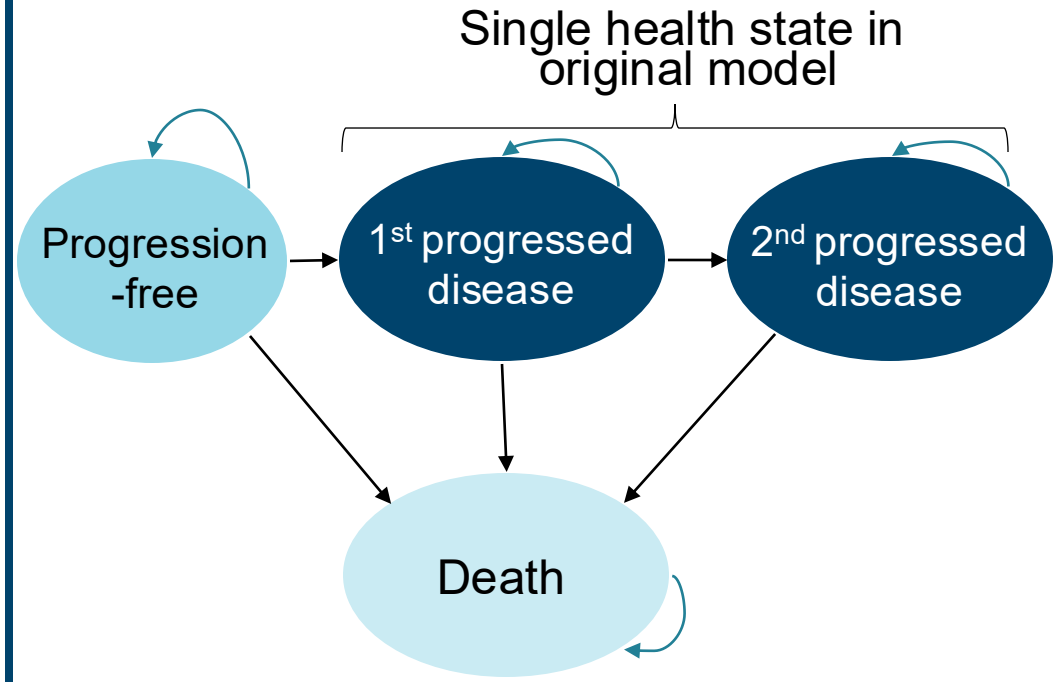
Key issue: 4-health state model – Extrapolating Study 1027

ACM1 committee considerations

- 4-state structure with 1st and 2nd progression would better reflect NHS sequences

Company response:

Implemented 4-state model structure



Source of transition probabilities

	PFS	Time-to-second progression	Post-second progression survival
1L Lorlatinib 2L Chemotherapy	CROWN PFS	CROWN time-to-second progression	2L PDC post-progression survival (TA628)
1L Alectinib/brigatinib 2L Chemotherapy	Lorlatinib CROWN PFS + ITC	CROWN time-to-second progression	2L PDC post-progression survival (TA628)
1L Alectinib/brigatinib 2L Lorlatinib 3L Chemotherapy	Lorlatinib CROWN PFS + ITC	Study 1027 Lorlatinib 2L PFS following a prior ALKi*	Study 1001 EXP3B:5 post-progression survival (TA628)

*Study 1001 (TA628) applied in scenario

EAG: implementation appropriate and aligns with preferences, but prefer different extrapolation for Study 1027

ALKi, anaplastic lymphoma kinase inhibitor; ITC, indirect treatment comparison; PDC, chemotherapy; PFS, progression-free survival

Key issue: Extrapolating study 1027 for time to 2nd progression

EAG disagree with company's extrapolation for time to 2nd progression transition

EAG:

- Company's exponential extrapolation of Study 1027 has worst fit to the data and lacks clinical plausibility
  - ↳ Implies time to 2nd progression is longer with chemotherapy than lorlatinib
  - ↳ Gamma extrapolation preferred for EAG base case
  - ↳ Weibull also plausible

Study 1027:

- Phase 4, single arm
- 71 people who progressed on 1st line alectinib (85%) or ceritinib (15%)
- Treated with 2nd line lorlatinib

Sequence (1st line → 2nd line)	2nd line PFS rate	Source	
Lorlatinib → chemotherapy	[redacted]	CROWN	
Alectinib/brigatinib → chemotherapy	[redacted]	CROWN	
Alectinib/brigatinib → lorlatinib	[redacted]	Study 1027 – exponential	← **Company**
Alectinib/brigatinib → lorlatinib	[redacted]	Study 1027 – Weibull	
Alectinib/brigatinib → lorlatinib	[redacted]	Study 1027 – gamma	← **EAG**

What is the committee's preferred extrapolation for time to 2nd progression?

See appendix for extrapolations

Key issue: Utility value for 2nd progressed disease health state

EAG apply higher utility value for people in 2nd progressed disease (PD2)

Company:

- Implementing 4-state model meant estimating more utility values for new states
- Applied utility of 0.46 to PD2 health state, sourced from TA628

EAG:

- 0.46 underestimates quality of life for patients in PD2 who are still on chemotherapy, especially considering the company model predicts 1.30 life-years for these people
- In TA628, committee preferred 0.46 value for people who progressed and were off treatment and 0.65 for people being treated beyond progression
- Company model does not allow separate on/off treatment utilities, so apply utility of 0.62 for people having chemotherapy after lorlatinib 2nd line, same as applied for people in 1st progressed disease (PD1) who are on chemotherapy

Which utility value should be applied in the PD2 health state?

See appendix for utility values

PD1, 1st progressed disease; PD2, 2nd progressed disease

Key issue: Proportion initiating 2nd line lorlatinib

ACM1 committee considerations

- Model assumes 86.8%* of all people who have alectinib/brigatinib 1st line have lorlatinib 2nd line, EAG clinical advice thought this reasonable
- CDF lead: only 40% alectinib/brigatinib currently go on to lorlatinib 2nd line in NHS
- Clinical expert: low uptake of 2nd line lorlatinib due to suboptimal NHS care

CDF lead on current NHS practice (post ACM1):

- **215–220** per year start 1st line alectinib/brigatinib
- **95** per year start 2nd or 3rd line lorlatinib
- So, **43–44%** subsequent lorlatinib rate
  - ↳ Relatively low % largely reflects attrition, particularly consequences of brain metastases
  - ↳ Unclear how suboptimal care affects 2L use

Company:
No change to base case for ACM2

EAG:

- EAG preferred assumption: 40%* of people have 2nd line lorlatinib after alectinib/brigatinib
- Proportion initiating lorlatinib 2nd line is key driver of ICER

What proportion of people should the model assume to have 2nd line lorlatinib?

*not adjusted for PFS events that are death. Model assumes 4.35% of PFS events were death in alectinib/brigatinib arm.

ALK, anaplastic lymphoma kinase; CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; NSCLC, non-small cell lung cancer.

Key issue: Treatment beyond progression

ACM1 committee considerations

- Clinical advice: treatment beyond progression expected for TKIs, usually 3 to 6 months
- More likely/longer duration if next option is chemotherapy
- Preferred assumption: time on treatment for lorlatinib, alectinib and brigatinib = PFS plus treatment beyond progression for 75.6%* for 3.5 months** (company base case for ACM2)

EAG:

- 75.6% unlikely for alectinib/brigatinib – implies delay in initiating 2nd line lorlatinib; <25% more plausible
- 5.7 months treatment beyond progression reasonable for lorlatinib, as chemotherapy is only 2nd line option
- Model implications: using ACM1 assumptions overestimates comparator costs in PD1 state

EAG preferred treatment beyond progression:

↳ Lorlatinib: 75.6% people for 5.7 months*

↳ Alectinib/brigatinib: 25% people for 3.5 months

↳ Also plausible: 55.4% people for 3.5 months (75.6% x 60% [2L chemo] + 25% x 40% [2L lorla])

TA909 assumption:

Lorlatinib: 5.7 months for 75.6%

Comparators: 3 months for 100%

TA628 assumption:

Lorlatinib: 3.5 months for 100%

How should treatment beyond progression be modelled for 1) lorlatinib 2) comparators?

*Derived from Study 1001

**Clinical advice from TA628

2L, 2nd line; PD1, 1st progressed disease; PFS, progression-free survival; TKI, tyrosine kinase inhibitor

Key issue: Conditional PAS discount for lorlatinib

ACM1 committee considerations

- Company offered lorlatinib with a new PAS, conditional on NICE approval at 1st line. The new PAS would then apply for both 1st and 2nd line lorlatinib (see appendix for diagram)
- **Company** argued that the new PAS should only apply in the intervention arm, and the comparator arm should use the existing PAS – made lorlatinib 1st line more cost-effective
- **EAG** argued that this incorrectly framed the decision, and the new PAS should be applied in both intervention and comparator arms
- **NICE**: Both methods have limitations. Company method best reflects current decision for committee; EAG method appropriate if optimising treatment pathway
- Committee took NICE advice to use company approach

EAG: Reiterate that company method incorrectly frames decision as 'before and after'

- Highlight that not all alectinib/brigatinib → lorlatinib use would be displaced by 1st line lorlatinib, so future appraisals may be significantly complicated as cost-effectiveness of comparators will differ depending on treatment pathway

NICE

How should the conditional PAS be implemented?

PAS, patient access scheme.

Key issue: Acceptable ICER

ACM1 committee considerations

- 'Due to uncertainties [see list], committee concluded an acceptable ICER would be towards the lower end of the range'

Company:

Company considers 20k threshold is overly cautious, as:

- Implemented all committee preferred assumptions, including some the company considered were conservative (see appendix)
- New model addresses key uncertainties around overall survival and treatment sequences issues

EAG:

- New model largely addresses risk of OS confounding due to treatment sequences, but use of separate, non-randomised sources means that risk not fully eliminated
- Still no direct evidence for OS benefit of lorlatinib – unresolvable with current data

Has the committee's preferred threshold changed given the updated company model?

NICE

ICER, incremental cost-effectiveness ratio; OS, overall survival.

Summary of company and EAG base case assumptions

Assumption	Company base case	EAG base case
Extrapolation of lorlatinib time to second progression from Study 1027	Exponential distribution	Gamma distribution
Progressed disease 2 utility value	For people who have 2nd line lorlatinib, 3rd line chemo, value = 0.46	For people who have 2nd line lorlatinib, 3rd line chemo, value = 0.62
Proportion initiating lorlatinib 2nd line	As original model: 86.8%	As clinical advice at 1st meeting: 40%
Treatment beyond progression	As committee preference at ACM1: • 75.6% of people get 3.5 months of treatment after progression • Same for lorlatinib and alectinib/brigatinib	• Lorlatinib: 75.6% get 5.7 months of treatment beyond progression • Alectinib/brigatinib: 25% get 3.5 months of treatment beyond progression
Conditional PAS application	As committee preference at ACM1, different PAS at 1st and 2nd line	As EAG preference at ACM1, same PAS at 1st and 2nd line

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 deterministic ICER:
- Between £20,000 and £30,000 per QALY gained

EAG base case deterministic ICER:
- Greater than £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
Time to 2nd progression	What is the committee's preferred extrapolation for Study 1027 – time to 2nd progression?
Utility values	Which utility value should be applied in the PD2 health state?
2nd line lorlatinib initiation	What proportion of people should the model assume initiate 2nd line lorlatinib?
Treatment beyond progression	• When would people stop taking lorlatinib in the NHS? • How should treatment beyond progression be modelled?
Conditional PAS	How should the conditional PAS be implemented?
ICER threshold	Has the committee's preferred threshold changed given the updated company model?
ICER	What is the committee's preferred ICER?
Managed access	• Is the committee's preferred ICER below the threshold? • If no, could key uncertainties be sufficiently resolved during a period of managed access?

ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; PD2, 2nd progressed disease.

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**

Managed access proposal and feasibility assessment

Company propose that, if routine commissioning is not an option, lorlatinib could enter the Cancer Drugs Fund for <3yrs. Next OS analysis of CROWN expected in 2027; final analysis expected Dec 2028.

Area	Rating	Comments / Rationale
Is the technology considered a potential candidate for managed access?	Yes	As a cancer drug, this technology is eligible for reimbursement through the CDF.
Are there outstanding uncertainties that could be resolved with further data collection?	High	A period of managed access would allow for further data collection on some key uncertainties, most notably further data cuts on OS.
Can data collection from ongoing clinical trials and RWE sources resolve relevant uncertainties?	Yes	Further data collection would be possible through the CROWN clinical trial as well as real world evidence generation through SACT.
Are there any other points to note that suggest RWE data collection may be beneficial or challenging in resolving uncertainties?	High	The SACT dataset could collect some useful information, in particular time on treatment and subsequent treatment as well as some information on the patient population (in combination with Blueteq criteria)
Are there any other substantive issues (excluding price) that are a barrier to a MAA?	No	It is expected that there are no substantive issues

EAG at ACM1: Further CROWN cuts of limited value due to treatment sequences issue

Supplementary appendix

NICE National Institute for Health and Care Excellence

Clinical evidence used in original model

	CROWN	Study 1001	PROFILE 1001 + 1005
Phase	3	1/2	1 and 2
Design	Randomised, open-label	Single arm, open-label	Single arm, open-label
Population	Advanced ALK+ NSCLC, no prior treatment	• EXP1 cohort: n=30 treatment-naïve • EXP3B to 5 cohorts: n=139 progression after ≥1 TKIs	ALK+ NSCLC with progression
Intervention	Lorlatinib	• EXP1: lorlatinib • EXP3B to 5: lorlatinib after previous TKI(s)	Chemotherapy following progression on crizotinib
Comparator	Crizotinib	None	None
Use in original model	Progression-free survival estimations for lorlatinib and with hazard ratio for comparator arm	• EXP1: long-term survival for lorlatinib • EXP3B to 5: Post-progression survival for comparator arm	Post-progression survival for chemotherapy in lorlatinib or comparator arms

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

CROWN primary outcome: Progression-free survival – independent assessment

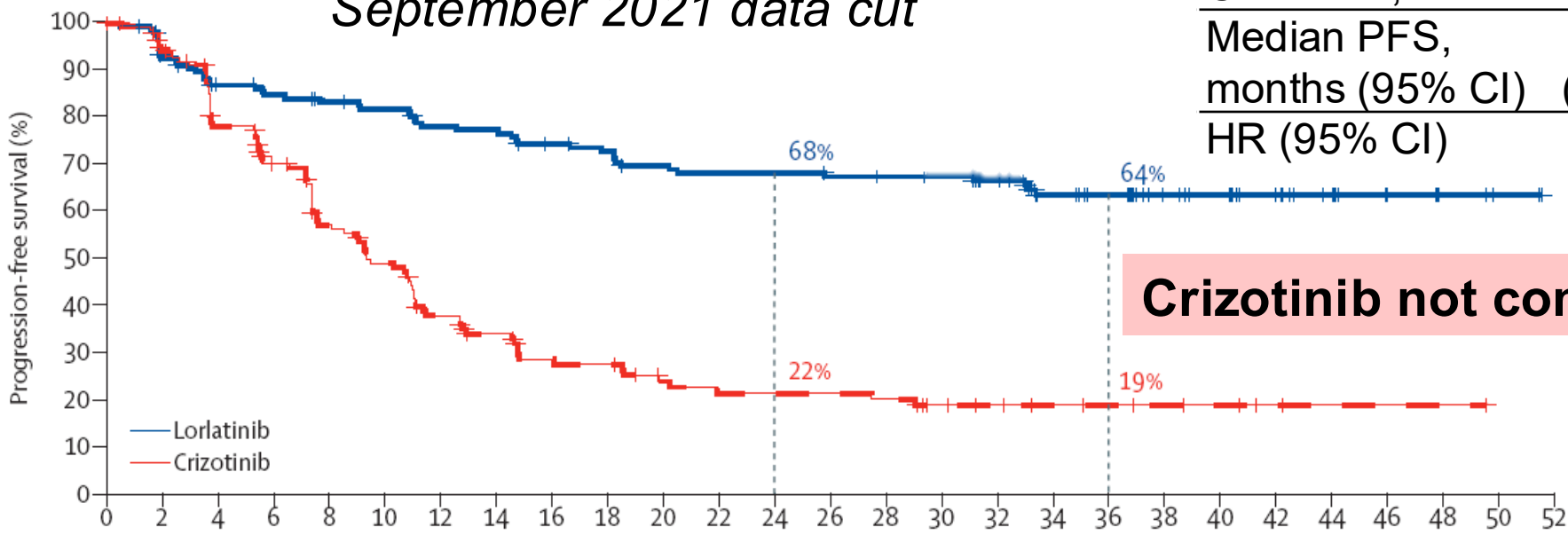
Presented in TA909 – Sept 21 data cut

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

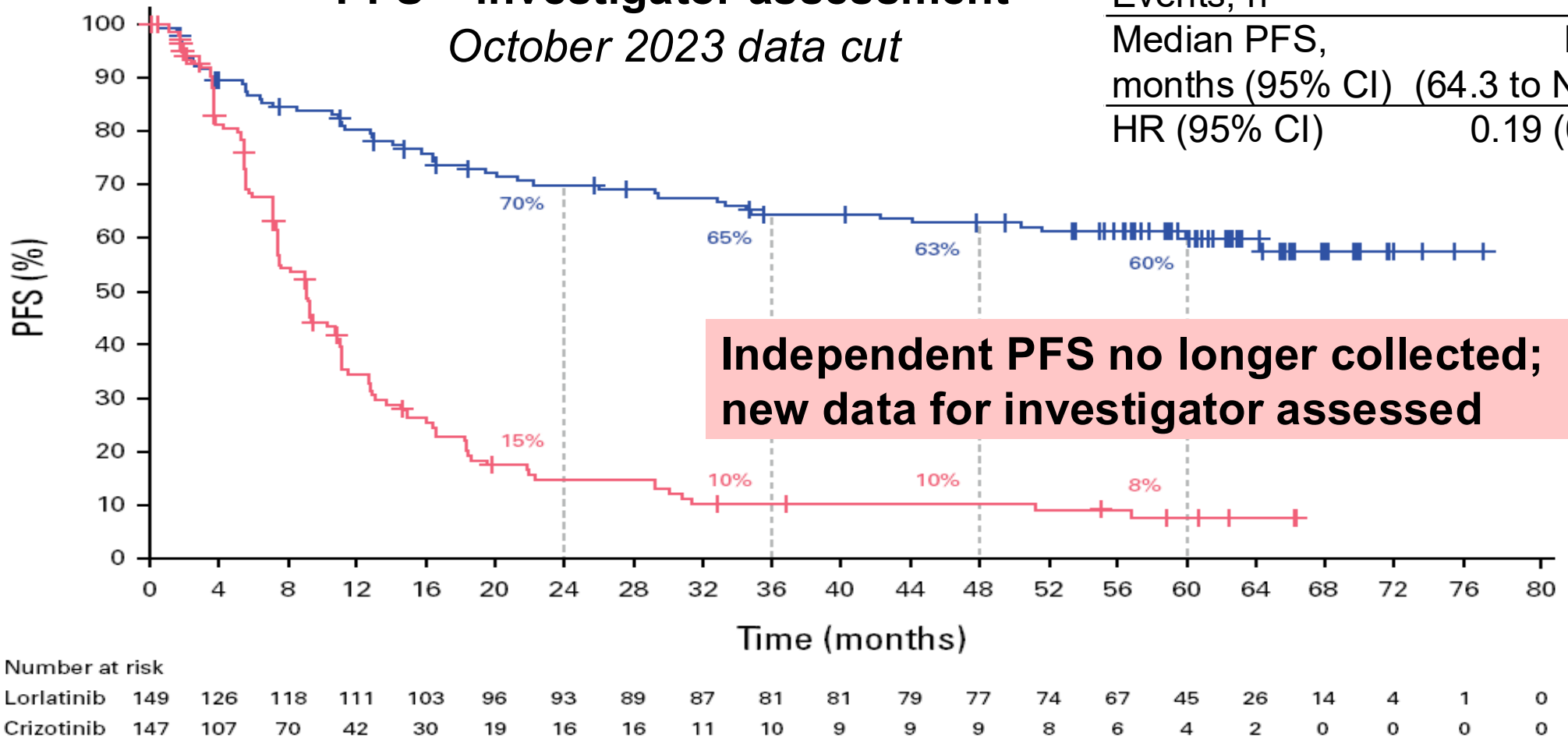
Improvement in PFS, but not as defined in primary endpoint

	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

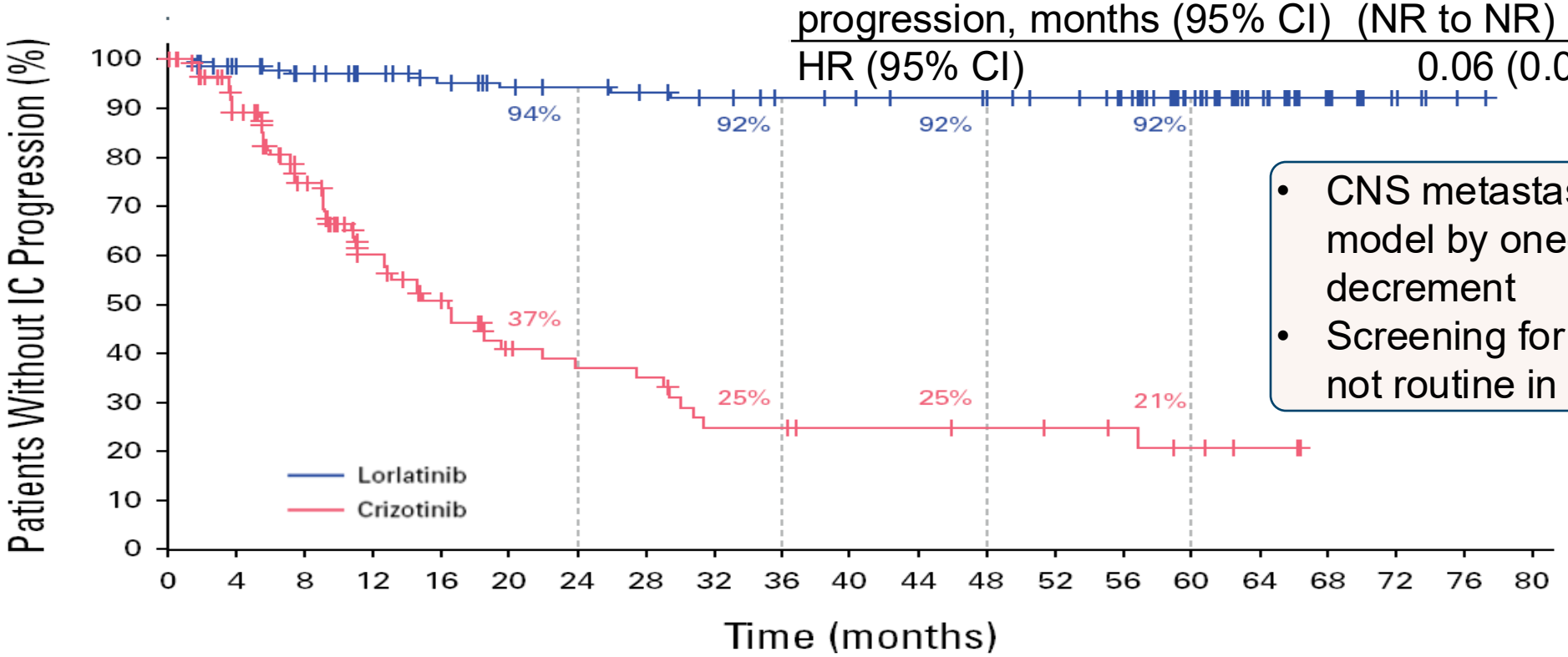
CROWN secondary outcome: Time to intracranial progression

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
- Screening for CNS metastases not routine in NHS

NICE

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

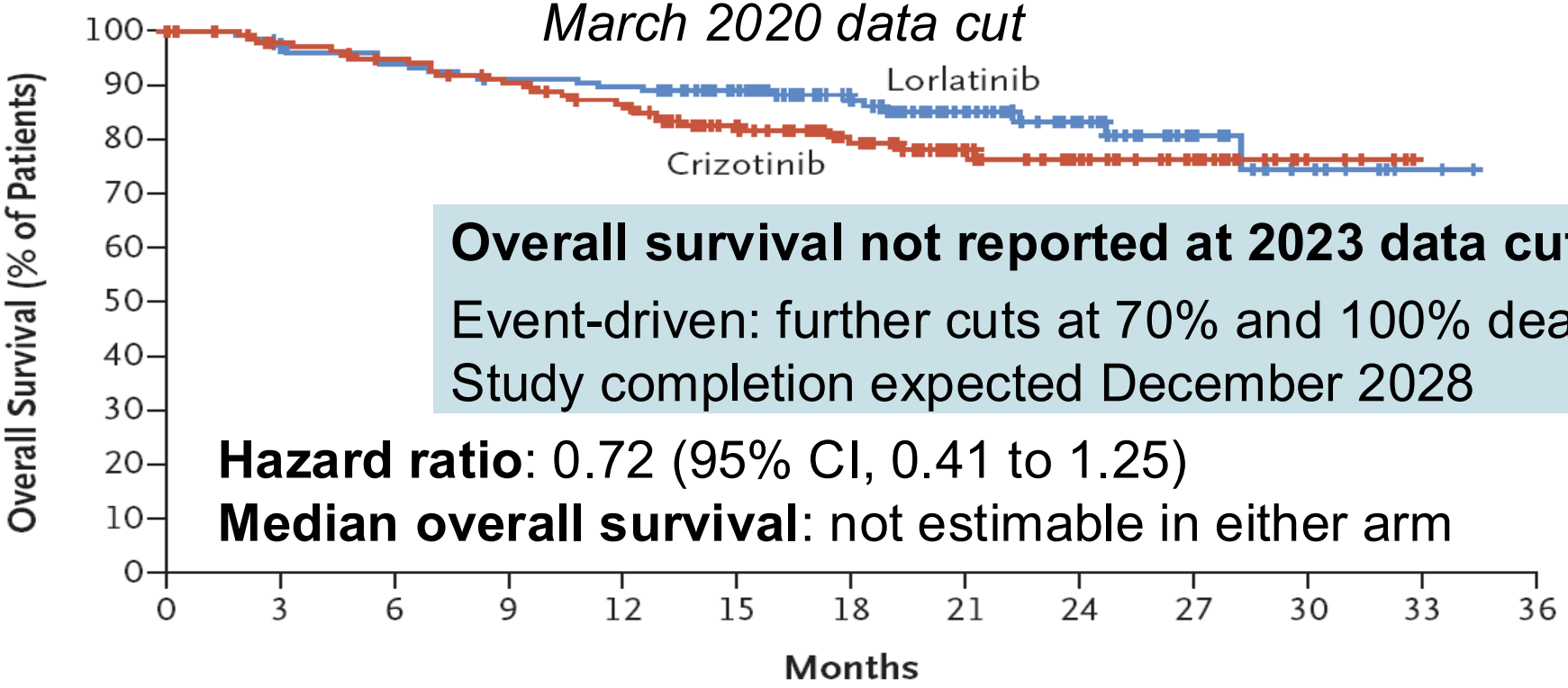
CROWN secondary outcome: Overall survival

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.

ACM1 – Preferred assumptions and requested analyses

Preferred assumptions:

- Lorlatinib used as reference arm to which hazard ratios are applied to model progression-free survival for comparators
- 36-month piecewise Gompertz curve used to extrapolate lorlatinib progression-free survival
- State-transition model used for post-progression survival in both arms
- For all treatments in the model, time on treatment should be equal to progression-free survival with treatment after progression of 3.5 months for 75.6% people
- Progression-free survival hazards waned to alectinib hazards after 10 years
- Health state utility values should align with the EAG's approach
- New conditional PAS discount for lorlatinib should apply only to the intervention arm of the model

Requested analyses:

- 4-state model structure that differentiates first progression from second progression

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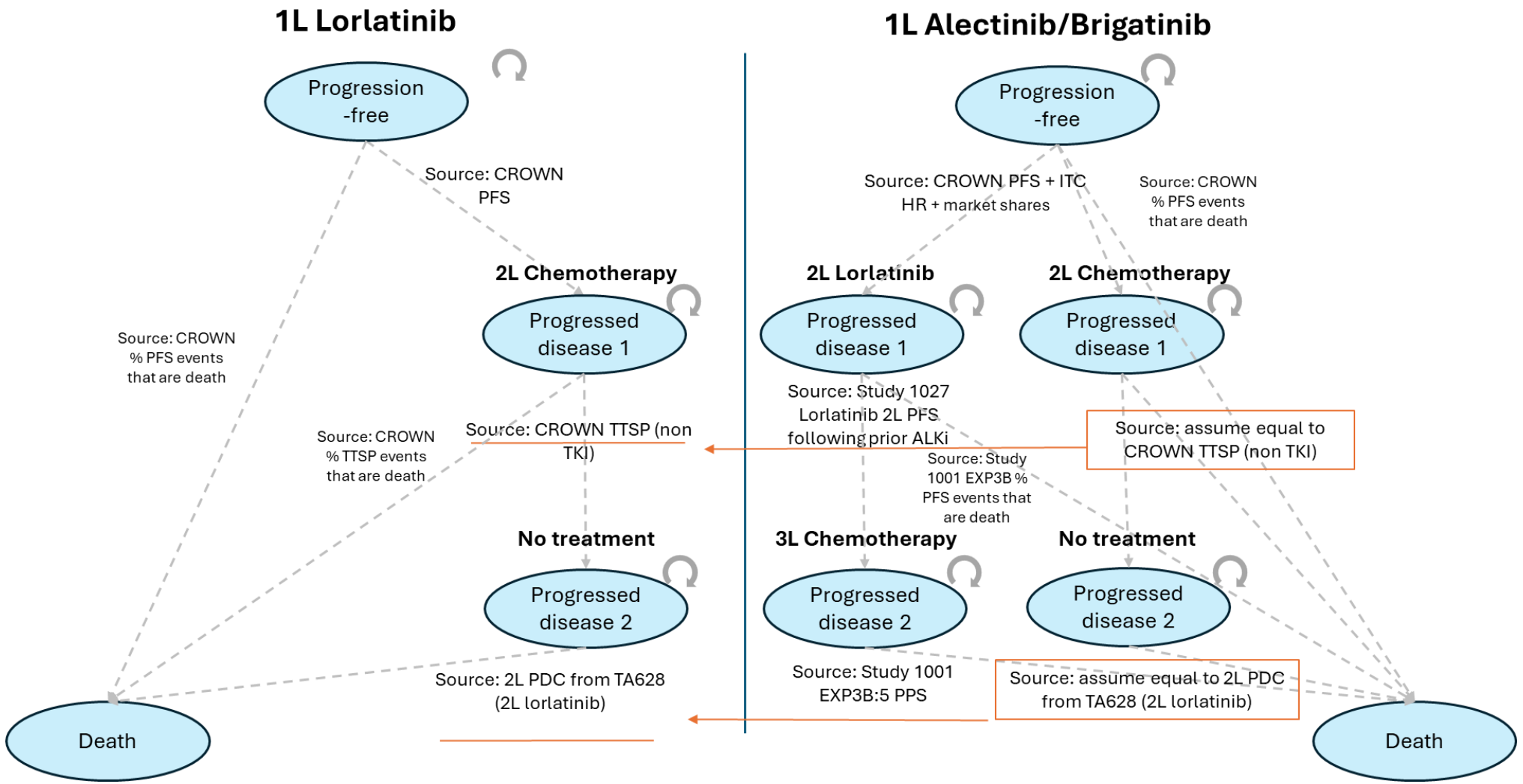
4 health state model structure and sources



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Study 1027 time to 2nd progression extrapolations

Study 1027 time to 2nd progression for alectinib/ceritinib → lorlatinib sequence

Fit statistics

Distribution	AIC	AIC rank	BIC	BIC rank
Generalised-gamma	281.42	1	288.21	1
Exponential	291.19	7	293.45	5
Weibull	289.84	5	294.37	6
Log-normal	283.80	2	288.32	2
Log-logistic	286.64	4	291.16	4
Gompertz	285.51	3	290.04	3
Gamma	290.84	6	295.37	7

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Utility values – company model

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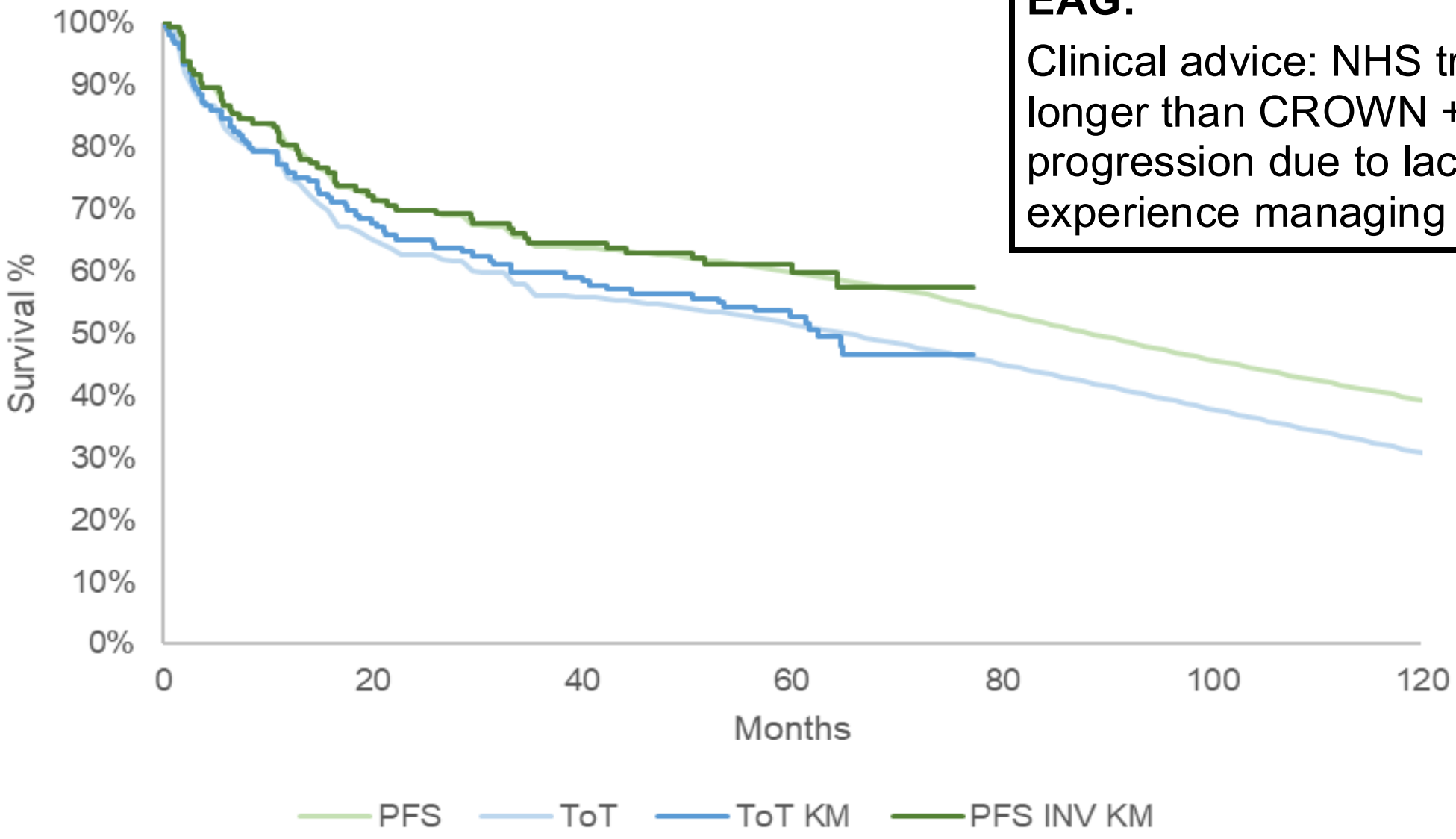
State, treatment sequence	On treatment	Off treatment	On treatment (beyond progression of previous line)
Progression-free			
Lorlatinib	0.793 (TA670)	N/A	N/A
Brigatinib	0.793 (TA670)	N/A	N/A
Alectinib	0.793 (TA670)	N/A	N/A
Progressed disease 1			
Lorlatinib → chemo	0.624 (TA670)	N/A	0.793 (TA670)
Brigatinib → chemo	0.624 (TA670)	N/A	0.793 (TA670)
Alectinib → chemo	0.624 (TA670)	N/A	0.793 (TA670)
Brigatinib → lorlatinib	0.725 (EAG assumption)	N/A	0.793 (TA670)
Alectinib → lorlatinib	0.725 (EAG assumption)	N/A	0.793 (TA670)
Progressed disease 2			
Lorlatinib → chemo → no treatment	N/A	0.460 (TA628)	N/A
Brigatinib → chemo → no treatment	N/A	0.460 (TA628)	N/A
Alectinib → chemo → no treatment	N/A	0.460 (TA628)	N/A
Brigatinib → lorlatinib → chemo	0.460 (TA628)	0.460 (TA628)	N/A
Alectinib → lorlatinib → chemo	0.460 (TA628)	0.460 (TA628)	N/A

EAG model changes these to 0.620

CROWN – lorlatinib time on treatment and progression-free survival

EAG:

Clinical advice: NHS treatment duration longer than CROWN + often beyond progression due to lack of 2nd line TKIs, experience managing adverse effects



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

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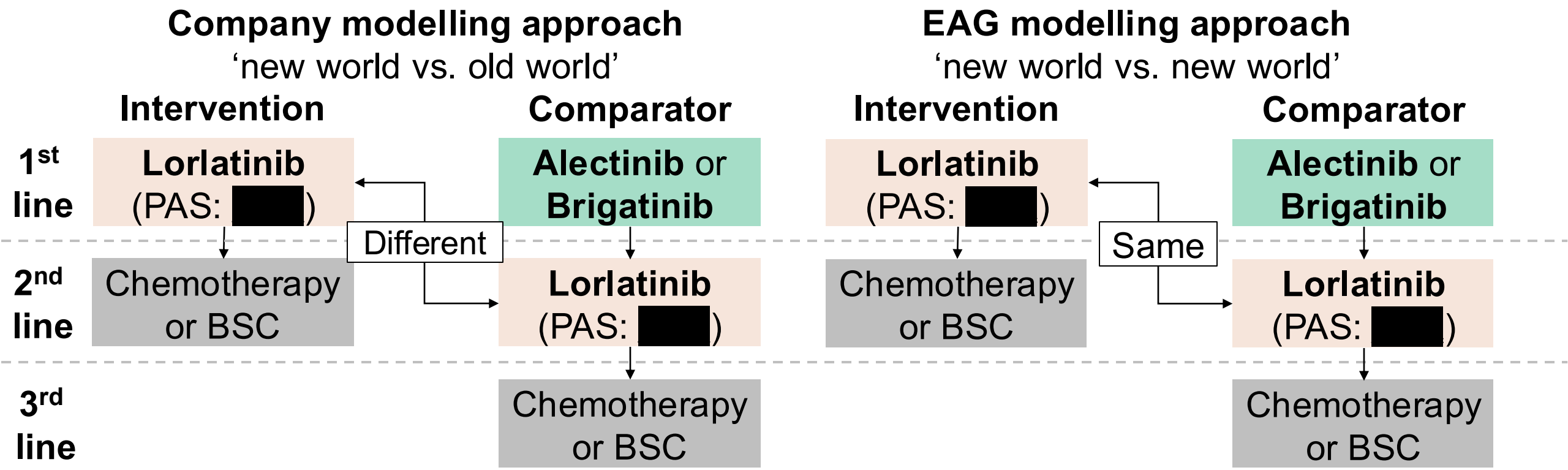
Key issue: Modelling conditional PAS for lorlatinib

Company and EAG disagree on methodological approach for implementing PAS

Background

- Lorlatinib has existing PAS of [redacted]
- Lorlatinib offered with PAS of [redacted] on condition of positive recommendation (would apply at 1st line and 2nd line if positive recommendation)



NICE Lorlatinib (1st line) **more cost-effective** | Lorlatinib (1st line) **less cost-effective**

Company's view of conservative assumptions

Assumption	Rationale on why this assumption is conservative for lorlatinib
STM approach for lorlatinib	Conservative post-second progression survival assumptions: post-second progression survival (after lorlatinib and chemotherapy) is the same as post-progression survival in the chemotherapy arm of the lorlatinib 2L submission, see comment 3.
TOT=PFS for lorlatinib	The assumption of TOT=PFS is conservative for lorlatinib, see comment 4. As highlighted in comment 5 the 5-year CROWN data showed a TOT<PFS relationship and therefore assuming TOT=PFS to align with committees preferred assumptions and additional treatment beyond progression for lorlatinib is a conservative assumption for lorlatinib given this adds additional cost for lorlatinib but not additional benefit
AEs of special interest for alectinib and brigatinib are not included	All AEs of special interest, regardless of grading, are included in the model for lorlatinib but not for alectinib or brigatinib and therefore this is a conservative assumption for lorlatinib. Additionally, in the model the management of AEs is costed separately from regular visits which is a conservative approach as UK clinicians have advised that managing AEs will not require additional resources as they would be considered during the regular visits and tests [30].
No reduction in resource use for lorlatinib 1L with longer term use	Resource use has been kept consistent over time in the model. However, it is anticipated that after several years of 1L lorlatinib treatment the frequency of healthcare resource use is likely to reduce. The company have validated this with HCPs who have confirmed that with long term 1L lorlatinib use they expect patients to require less frequent healthcare visits and monitoring. Therefore, this represents a conservative assumption with respect to lorlatinib.

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