Cost slides for public– no confidential information

Lead team presentation

Alectinib for untreated anaplastic lymphoma kinase-positive advanced non-small cell lung cancer – STA

1st Appraisal Committee meeting

Cost Effectiveness

Committee D

Lead team: Dr Nabeel Alsindi, Susan Dutton, Malcolm Oswald

ERG: BMJ-TAG

NICE technical team: Lucy Beggs, Christian Griffiths

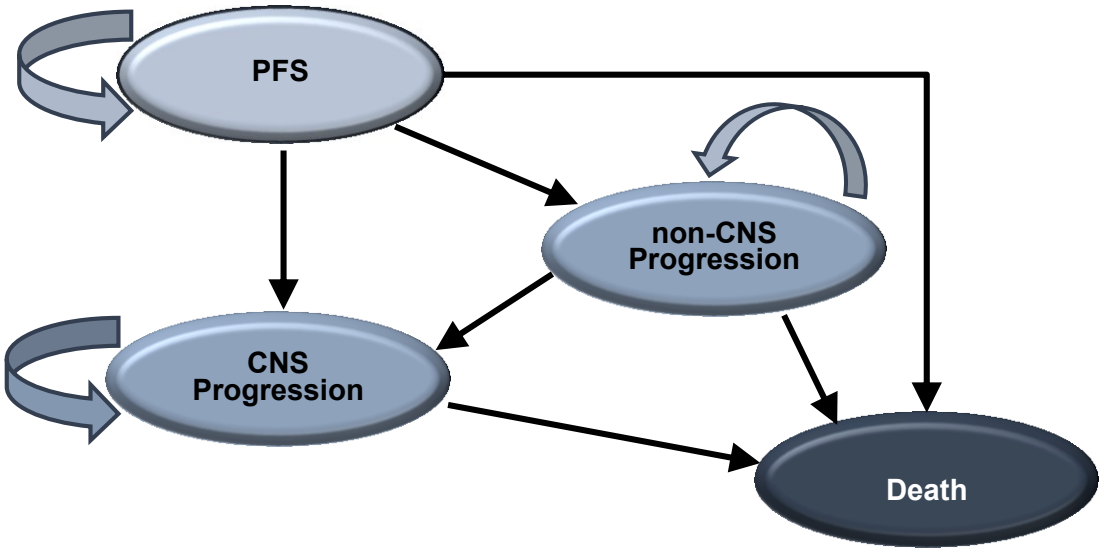
8th March 2018

Key issues

Cost effectiveness:

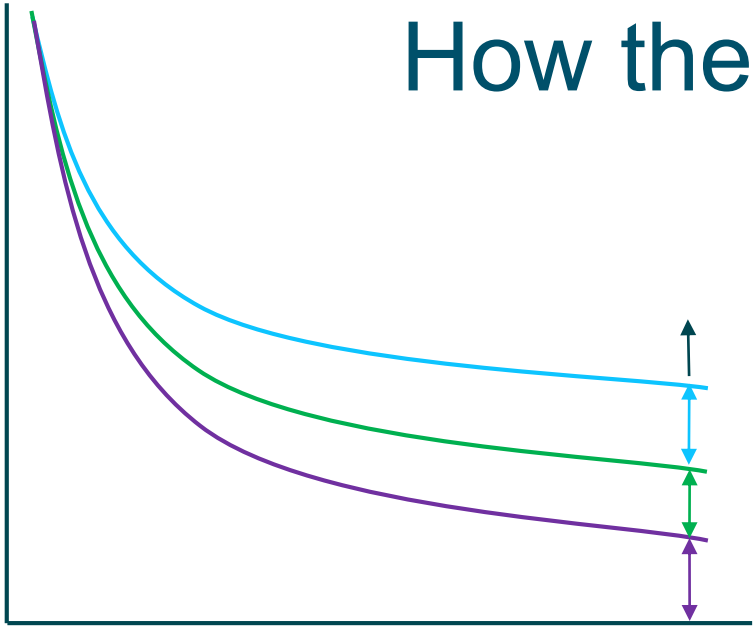
- Distribution of subsequent treatments after progression → most plausible assumptions?
- Most appropriate progression-free survival extrapolation assumptions → company chose 18 month Kaplan-Meier data cut-off point
- Most appropriate overall survival extrapolation → company use exponential distribution, ERG prefer KM+exponential tail
- Most appropriate management of CNS events: base-case assumes 100% stereotactic radiosurgery (SRS) & steroids. Company scenario analysis assumes 100% people receive steroids, 23% receive SRS & 77% receive whole brain radiotherapy (WBRT) → ERG explore scenario analysis without WBRT
- Are there any health benefits that have not been captured?
- Considerations about equalities, end of life and Cancer Drugs Fund

Company's model



- Comparison of alectinib versus crizotinib (using evidence from ALEX)
- Cohort based area-under-the-curve (AUC) or 'partitioned survival' model
- 4 health states: progression-free survival, CNS progressed disease, non-CNS progressed and death
- 30 year time horizon (considered a 'lifetime' horizon given typical age at diagnosis and expected survival times)
- 3.5% annual discount rate applied to costs and benefits; weekly cycle with half-cycle correction; NHS and PSS perspective

How the model works



Death	= 1 – P(OS)
CNS progression	= P(OS) – P(CNS-PFS)
Non-CNS progression	= P(CNS-PFS) – P(PFS)
Progression-free	= P(PFS)

- Proportion of patients in each health state derived from proportion of patients taken from PFS, CNS-PFS and OS curves
- Patients start in the progression-free survival health state
- Patients move forward through model to any ‘later’ state:
  - Can move from PFS to non-CNS progressed, CNS progressed or death
  - Can move from non-CNS progressed to CNS progressed or death
  - Can move from CNS progressed to death

Non-CNS progression & censoring

- Non-CNS progression events were not censored in CNS-PFS analysis
- CNS-progressed state could hence include both:
  1. CNS-progressions as the first progression event (primary event)
  2. CNS-progressions after systemic progression event (secondary event)
- Company justify not censoring: *'When such censoring was applied, the CPFS* [CNS-PFS] *curves crossed the OS curves, which produce implausible outcomes (negative population of the CPFS* [CNS-PFS] *health state), given the partitioned survival model structure.'*

- ERG assumed that all first CNS events were also systemic progressions, and therefore captured in the PFS curve
- ERG not concerned that secondary CNS events aren't explicitly modelled because in the model a CNS progression always 'trumps' a systemic disease progression → costs & QALYs appropriately captured
- ERG accepts company's justification for not censoring non-CNS events

Clinical data in the model

- ALEX = data source for clinical outcomes, adverse events & quality of life
- Company base-case PFS & CNS-PFS uses IRC RECIST & CNS-RECIST
- Median OS not met in either arm
- Median investigator-assessed PFS not met in alectinib arm

Extrapolation of PFS, CNS-PFS and overall survival curves

- Choice of extrapolation distribution based on…
  - Statistical fit assessed using AIC & BIC
  - Goodness of fit also assessed visually
  - Clinical plausibility assessed through visual inspection and external validation against available longer term data
- Non-proportional hazards for OS & PFS (log cumulative hazard plots cross)

ERG agrees with independent fit approach (although notes that proportional hazards assumption wasn't assessed for 'RECIST only' CNS-PFS data)

Overall survival extrapolation

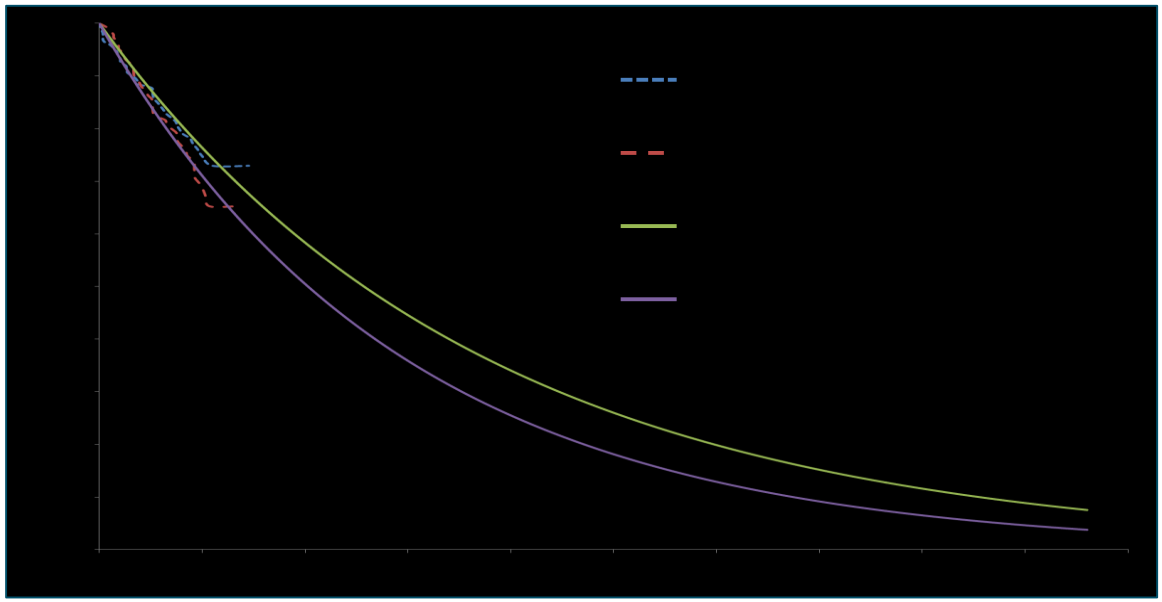
	Alectinib		Crizotinib	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	**246.59**	**249.61**	**234.24**	**237.26**
Weibull	247.98	254.03	232.71	238.74
Log-normal	247.97	254.02	230.88	236.91
Gamma	249.79	258.86	232.79	241.84
Log-logistic	247.91	253.96	232.10	238.13
Gompertz*	248.59	254.63	234.72	240.76

*Gompertz did not converge for alectinib ∴ excluded

- Distributions assessed against visual fit to ALEX Kaplan-Meier data
- None of the extrapolations for crizotinib meet the 4 year overall survival for people treated with crizotinib in the PROFILE 1014 trial (expected as the PROFILE population healthier than ALEX)
- Gamma = best fit to PROFILE data but implausible ↑ hazard after 140 months
- Exponential is second best fit to PROFILE data → plausible but conservative

Exponential extrapolation used as base case for alectinib & crizotinib

Overall survival extrapolation



Company's base case = exponential extrapolation

ERG comment:

- Subsequent treatment has substantial impact on OS → uncertainty as only 41% subsequent treatment data available from ALEX
- ALEX does not provide robust evidence of a long term OS benefit
- Although exponential curves conservative, they imply proportional hazards; company have demonstrated assumption not met
- ERG explored Kaplan-Meier with exponential tail (caveat that 18 month Kaplan-Meier cut-off is arbitrary)

Progression-free survival extrapolation

Progression-free survival based on IRC RECIST and CNS-RECIST

	Alectinib		Crizotinib	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	381.93	384.96	384.40	387.42
Weibull	378.95	385.00	384.30	390.34
Log-normal	371.85	377.90	370.73	376.77
Gamma	369.76	378.83	369.26	378.31
Log-logistic	376.07	382.12	375.01	381.04
Gompertz	383.93	389.98	386.40	392.44

- Company's original base-case was based on investigator-assessed PFS; using Kaplan-Meier data extrapolated with an exponential tail
- Company updated model structure at clarification
- Company's updated PFS curve was *'projected using [Kaplan-Meier] + exponential for consistence with previous modelling of PFS and as this still provided a good fit to this endpoint'*

Kaplan-Meier with exponential tail used as base case extrapolation

Progression-free survival extrapolation

REDACTED
Commercial in confidence

Company's preferred base-case: Kaplan-Meier with exponential tail PFS (IRC; CNS RECIST & RECIST)

ERG comment:

- ALEX survival outcomes likely to be an overestimate (committee's consideration of PROFILE 1014 in TA500)
- ERG agrees with using exponential tail as conservative
- Consequence of using exponential tail after 18 months is that hazard ratio between treatments becomes proportional; inconsistent with company's assessment of proportional hazards
- ERG considers 18 month cut-off point for Kaplan-Meier data arbitrary

CNS-PFS extrapolation

Company's base case: IRC RECIST & CNS-RECIST

	Alectinib		Crizotinib	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**
Exponential	298.93	301.95	372.19	375.21
Weibull	299.56	305.61	368.48	374.51
Log-normal	297.25	303.29	353.97	360.01
Gamma	**298.98**	**308.05**	**352.46**	**361.51**
Log-logistic	298.89	304.94	358.53	364.57
Gompertz	300.93	306.98	373.87	379.90

Company modelled Gamma distribution because it captured the "*levelling off of cumulative CNS metastasis incidence in the long term, demonstrated by the poster presented by Betts et al. at the 2016 AMCP Managed Care & Specialty Pharmacy Annual Meeting in San Francisco*".

Gamma distribution used as base case extrapolation

Base-case CNS-PFS extrapolation

REDACTED
Commercial in confidence

Kaplan-Meier data for CNS-PFS measured by IRC CNS-RECIST & RECIST and IRC RECIST only

Company's preferred base-case: Gamma extrapolation for CNS-PFS (IRC; CNS RECIST & RECIST)

ERG comment: Gamma distribution was one of the worst fitting curves (based on AIC/BIC) → lognormal or log-logistic appear better, but updating had negligible impact

Base case utilities

State	Utility (SE)	Justification
Progression-free	0.814 [redacted]	Derived using mixed-model from ALEX EQ-5D data
Progressed disease	0.725 [redacted]	As above
CNS-progressed disease	[redacted] 0.52 [redacted]	Peters et al. (2016) & Roughley et al. (2014). SE based on assumption.

ERG comment:

- Roughley et al. do not report utilities for non-CNS progressed disease → cannot compare with value in ALEX and check consistency
- ERG explored CNS progression utility in scenario analysis

Clinical experts: CNS-progressed disease utility value looks reasonable

Acquisition and administration costs

- Alectinib and crizotinib both have confidential PAS discounts
- Both-administered as full pack at lung cancer clinic (every 4 weeks)
- Model incorporates 'wastage' if a patient dies/discontinues
- 'No wastage' assumption explored as scenario analysis

Drug	Concentration	Pack volume	Dose p/pack	Cost p/pack	Source	Cost p/ administration
Alectinib	150 mg	224	33,600 mg	£5,032.00	BNF	£9.20 (pharmacist; 12 min every 4 wks)
Crizotinib	250 mg	60	15,000 mg	£4,689.00	BNF	

ERG comment:

- Crizotinib pack = 30 day treatment, alectinib pack = 28 day treatment
- Cycle = 28 days ∴ 2 days crizotinib wasted (not accounted for in 'wastage')
- ERG amended model so crizotinib bought every 30 days (instead of 28)

ERG comment on resource use

- Cost estimations generally correct. However, ERG updated crizotinib costing so one pack was purchased every 30 days instead of 28 days
- Clinical experts indicated that frequency of oncologist visits was underestimated → ERG ran additional analysis with visits every 4 weeks
- Company base-case assumes stereotactic radiosurgery (SRS) used for 100% patients with CNS metastases. All patients additionally received steroids
- However, SRS only available for patients with ≤2 metastatic sites
- Company scenario analysis: 23% receive SRS, 77% receive whole-brain radiotherapy (WBRT); all patients receive steroids
- ERG clinical expert view: 23% receive SRS + steroids, 77% steroids only

Treatments given after disease progression

	Alectinib		Crizotinib	
Treatment	**n**	**%**	**n**	**%**
Any subsequent anti-cancer tx	40	59%	44	42%
Any TKI	19	48%	36	82%
Ceritinib	4	10%	14	32%
Alectinib	0	0%	10	23%
Crizotinib	9	23%	2	5%
Other	6	13%	10	23%
Platinum compound	19	48%	6	13%
Antimetabolite	17	43%	6	13%
Taxane (paclitaxel, docetaxel)	3	8%	1	2%
Immunostimulant (nivolumab)	2	5%	0	0%
Angiogenesis inhibitor	2	5%	0	0%
Other	4	10%	1	2%
Patients on TKIs		**29%**		**72%**
Patients on non-TKIs		**71%**		**28%**

- Subsequent treatments in the company's model
- Data from 2nd/3rd line subsequent treatments from ALEX merged and reweighted to account for patients with data not captured

Subsequent treatment resource use

- Company base-case: weighted subsequent treatments (ALEX distribution)
- Subsequent treatment utilities explored through scenario analysis
- Scenario analysis of distribution based on UK clinical practice
- Assumes 100% patients receive 2L treatment & treatments mutually exclusive
- Mean time on subsequent treatment taken from trials & literature
- Subsequent therapies assumed same regardless of CNS metastasis

ERG comment:

- Only 41% of ALEX had subsequent treatment data captured
- Clinical experts: subsequent TKI treatment not usually given if CNS metastases has developed
- As alectinib has protective effect on CNS, likely that ↑ proportion of alectinib arm would receive subsequent TKI compared to crizotinib arm
- ERG ran 3 scenario analyses that reflected distribution of subsequent treatments in clinical practice

Company results

based on list prices

Based on IRC CNS-RECIST & RECIST (company's base case)

	Total costs	Total LYG	Total QALYs	Inc costs	Inc LYG	Inc QALYs	ICER £/QALY
Crizotinib	£135,955	4.25	2.61				
Alectinib	£219,643	5.17	3.77	£83,688	0.93	1.15	£72,544

Probabilistic sensitivity analysis results (1000 iterations):

	Costs		QALYs		ICERs	
	Base case	PSA	Base case	PSA	Base case	PSA
Crizotinib	£135,955	£132,761	2.61	2.61		
Alectinib	£219,643	£216,573	3.77	3.77	£72,544	£72,651

Key drivers in deterministic sensitivity analysis = health state utility value of CNS progression, progressed disease costs & utilities, progression-free survival costs & utilities

ERG preferred range of ICERs

based on list prices

	Assumption	ICER	Cumulative ICER*
1	Company's corrected base-case using RECIST outcomes	-	£75,079
2	Extrapolating OS curves using Kaplan-Meier + exponential tails	-	£80,146
3	Frequency of oncologist visits = every 4 weeks	£75,689	£80,803
4	CNS event management: 100% patients receive steroids, 23% patients receive SRS, 77% patients receive WBRT	£78,450	£84,407
% patients receiving subsequent TKI (alectinib vs crizotinib):			
5 (ERG's preferred base-case range)	a) 71% vs 31.4%	£126,265	**£142,060**
	b) 31.4% vs 31.4%	£116,501	**£132,635**
	c) 19.1% vs 31.4%	£113,099	**£129,324**

*cumulative *ICERs incorporate preceding assumptions. ICERs 5a-c are the ERG's range of preferred base-case ICERs; these ICERs incorporate assumptions 1-4*

Company scenario analyses

1. Progression-free survival extrapolations
2. Post-progression utilities
3. Subsequent treatment distributions
4. CNS-PFS extrapolations
5. Overall survival extrapolations
6. Capping of OS and PFS treatment effect duration
7. Adverse event disutilities
8. Wastage assumption
9. % of patients receiving SRS* vs corticosteroids at CNS progression
10. PFS/CNS-PFS measurement and modelling

*SRS, stereotactic radiosurgery

Company scenario analysis results (1)

		Alectinib		Crizotinib		
	Scenario	Total QALYs	Total costs	Total QALYs	Total costs	ICER
	Base-case	3.77	£219,643	2.61	£135,955	£72,544
1	Exponential	3.77	£223,070	2.61	£134,675	£76,155
	Weibull	3.83	£268,958	2.61	£130,927	£112,485
	KM+Weibull	3.83	£266,779	2.61	£131,972	£110,302
2	1 PPS utility (ALEX)	3.77	£219,643	2.61	£135,955	£72,544
	2/3rd line PPS utilities	3.24	£219,643	2.36	£135,955	£95,820
3	Clinical practice	3.77	£234,346	2.61	£149,575	£73,483
4	Exponential	3.59	£220,376	2.53	£136,027	£79,142
	Weibull	3.73	£219,773	2.50	£134,534	£69,122
	Log-normal	3.77	£219,641	2.54	£136,334	£67,876
	Log-logistic	3.77	£219,643	2.56	£136,272	£68,932
	KM with Gamma tail	3.75	£219,712	2.61	£135,960	£73,673

Company scenario analysis results (2)

		Alectinib		Crizotinib		
	Scenario	Total QALYs	Total costs	Total QALYs	Total costs	ICER
5	Weibull	4.32	£223,668	2.02	£130,952	£40,238
	Log-normal	6.12	£237,942	3.05	£139,093	£32,194
	Gamma	5.47	£232,250	3.36	£142,426	£42,607
	Log-logistic	5.43	£231,842	2.76	£135,902	£35,917
6	3 years	3.39	£187,198	2.61	£135,955	£66,065
	5 years	3.53	£204,416	2.61	£135,955	£75,095
	7 years	3.61	£212,495	2.61	£135,955	£76,668
	10 years	3.69	£217,286	2.61	£135,955	£75,792
7	AE disutility	3.77	£219,643	2.61	£135,955	£72,533
8	No wastage	3.74	£218,238	2.66	£130,944	£80,450
9	76.74% steroid use	3.77	£213,432	2.61	£126,173	£75,640
10	Original modelling	3.74	£219,941	2.71	£149,539	£68,508
	RECIST only	3.82	£225,992	2.80	£154,013	£70,514

Innovation considerations

- **Company** considers alectinib to be innovative:
  - Crizotinib = 69% patients progress within 18 months → unmet clinical need
  - Granted Promising Innovative Medicine designation by Medicines & Healthcare Products Regulatory Agency (MHRA)
  - Early Access to Medicines Scheme (EAMS) also approved by MHRA → significant advance over other ALK inhibitors
  - Delays CNS progression
- **ERG** has concerns that long-term clinical effectiveness of alectinib not adequately captured in ALEX to assess clinical plausibility of extrapolations in model
- **Clinical experts** consider that alectinib's role in delaying CNS progression may need special consideration
- **Patient and professional groups** did not consider that benefits would not be captured by QALY

End of life considerations

- Company does not consider alectinib to meet end of life criteria
- Standard care for patients with untreated ALK-positive NSCLC = crizotinib

Life expectancy:

- Median OS of patients on crizotinib in ALEX not reached; 12-months survival rate = 82.5% (95% CI: 76.1%, 88.9%)
- Median OS for results reported in literature range from 30.9 to 51.1 months (estimates from company submission)

Extension to life:

- ALEX data immature, but no significant difference between OS in alectinib and crizotinib (HR: 0.76, 95% CI: 0.48, 1.20)
- Incremental life year gained in company's economic model (alectinib vs crizotinib) = 0.93

Committee decision-making: CDF recommendation criteria

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to **clinical uncertainty**

1. Is the model robust for decision making?

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

Consider recommending entry into CDF

Key issues

Cost effectiveness:

- Distribution of subsequent treatments after progression → most plausible assumptions?
- Most appropriate progression-free survival extrapolation → company chose 18 month Kaplan-Meier data cut-off point
- Most appropriate overall survival extrapolation → company use exponential distribution, ERG prefer KM+exponential tail
- Most appropriate management of CNS events → base-case assumes 100% stereotactic radiosurgery (SRS) & steroids. Company scenario analysis assumes 100% people receive steroids, 23% receive SRS & 77% receive whole brain radiotherapy (WBRT) → ERG explore scenario analysis without WBRT
- Are there any health benefits that have not been captured?
- Considerations about equalities, end of life and Cancer Drugs Fund