Clinical 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

Background and Clinical Effectiveness

Committee D

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ERG: BMJ-TAG

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Key issues

Clinical effectiveness:

- Immaturity of the data and impact on overall survival conclusions
- Quality, risk of bias and generalisability of ALEX trial which compared alectinib with crizotinib given:
  - Different measurements of progression-free survival and CNS- progression-free survival (investigator, IRC RECIST or IRC RECIST & CNS-RECIST)
  - Treatment of asymptomatic disease after progression
  - Missing data on subsequent treatment distribution

Non-small cell lung cancer (NSCLC)

- Usually no early signs, presents in advanced stages III/IV (75%)
- Symptoms include cough, breathlessness, blood in sputum, weight loss
- 2 histological types: non-small cell (NSCLC) and small cell
- Approximately 40% to 50% of patients with NSCLC develop central nervous system (CNS) metastases which are associated with poor median survival (4 to 9 months with chemotherapy, 2 months if untreated)
- Anaplastic lymphoma kinase (ALK) fusion genes are chromosomal alterations believed to be involved in tumour growth, and occur most commonly in tumours with adenocarcinoma histology (non-squamous)
- ~5% people with advanced NSCLC have ALK mutation (1170 people in England)

ERG comment:

- ALK variant: younger, female, less associated with smoking history
- As a result, may not be picked up by 'high risk' screening programs

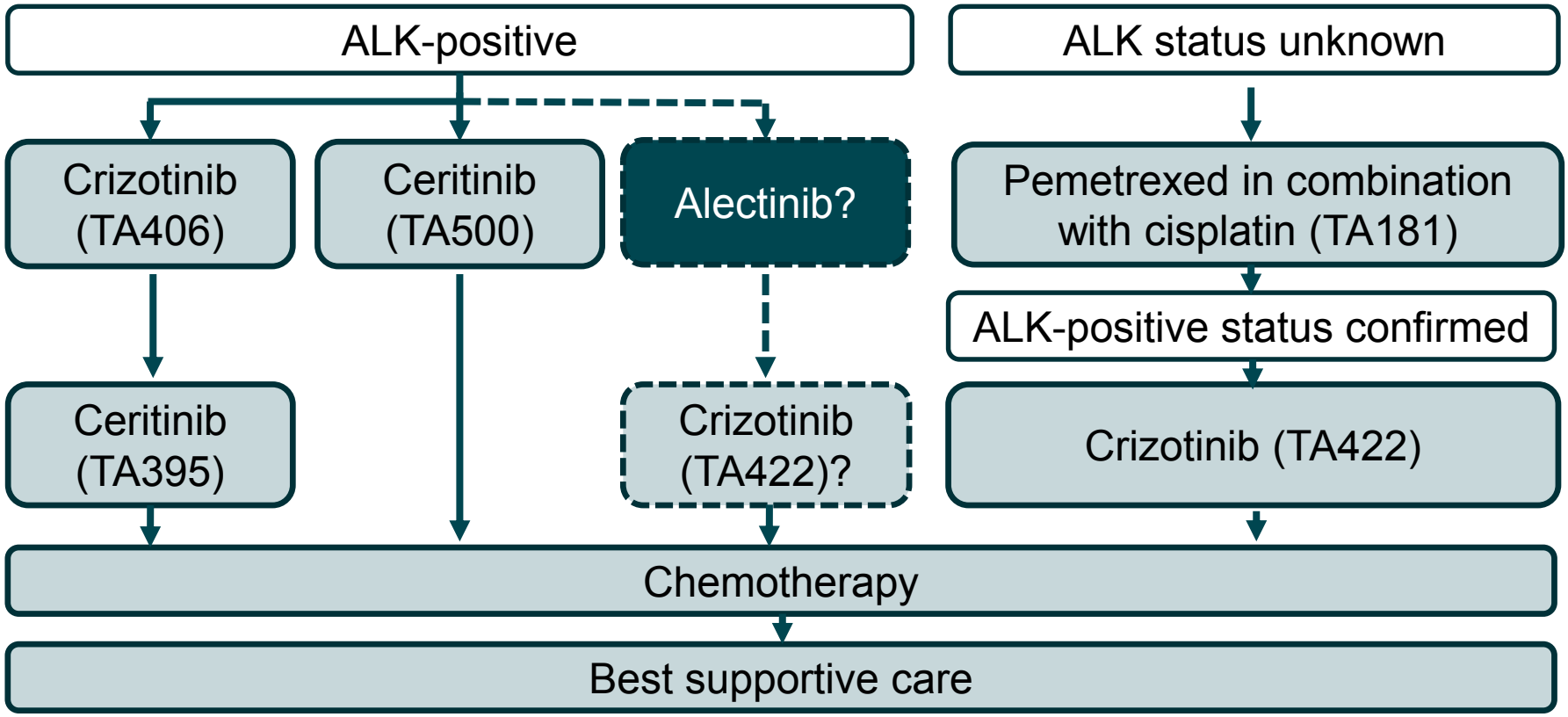
Patient perspectives

- Submission: Roy Castle Lung Cancer Foundation
- Non-small cell lung cancer (NSCLC) is a disease with no cure that can lead to physical and psychological distress
- Anaplastic Lymphoma Kinase (ALK) gene rearrangement found in a very few lung cancer patients
- New target therapies offer much better options for these patients
- Compared with crizotinib, alectinib has superior efficacy and lower toxicity

Clinician perspectives

- Submissions: British Thoracic Oncology Group, and 3 clinical experts
- “Brain metastases are uniquely difficult to treat and palliate”
- ALEX trial:
  - Only 1% UK population (45% Asian)
  - Sample may be healthier than UK → may over-estimate survival gains
  - But survival gains expected given brain disease control
- Compared to crizotinib, alectinib:
  - Is better tolerated (→ reduced resource use)
  - Has better intracranial disease control and progression-free survival
  - Enables better quality of life
  - Leads to fewer neurological investigations and interventions
  - Considered a “paradigm shift” because of role in brain metastases
- Stopping rule: “when radiological and clinical progression on treatment”
- Same oral administration as crizotinib – minimal new resources/ education

Current treatment for advanced NSCLC



ERG comment:

- Treatment pathway in line with NICE pathway for NSCLC
- Ceritinib now available for first line use (TA500) → uncertainty about effect on treatment pathway

Alectinib (Alecensa)
Roche

Mechanism of action	2nd generation tyrosine kinase inhibitor (TKI)
Marketing authorisation	Alectinib as a monotherapy is indicated for the first line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC)
Administration	Oral
Dose	600 mg (4 x 150 mg capsules) twice daily
Duration of treatment	Continue until disease progression or unacceptable toxicity
Cost (list price)	£5,032 per 224 capsule pack (28 day supply) Patient access scheme has been accepted by Department of Health. This provides a simple discount to list price.

Decision problem

	Scope	Company?
Population	Adults with untreated anaplastic lymphoma kinase-positive (ALK-positive) advanced non-small-cell lung cancer (NSCLC)	✓
Intervention	Alectinib	✓
Comparators	Crizotinib	✓
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	✓

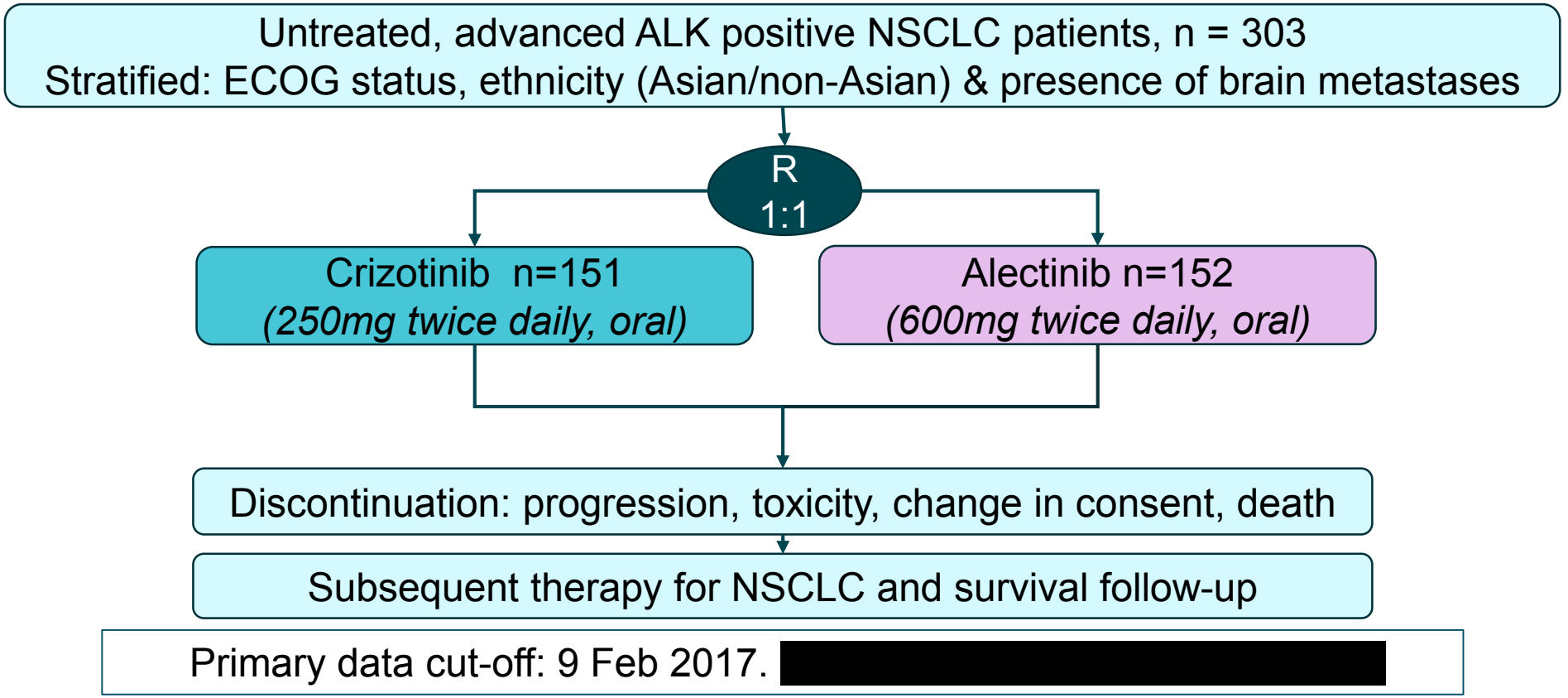
Key trial: ALEX

Design	Phase III, open-label, multi-centre randomised controlled trial
Population	Patients with previously untreated advanced ALK-positive NSCLC, n=303
Intervention	Alectinib, 600 mg twice daily, n=152
Comparator	Crizotinib, 250 mg, twice daily, n=151
1◦ outcome	Progression-free survival (investigator assessed)
Secondary outcomes	• Overall response rate • Duration of response • Time-to-central nervous system (CNS) progression • Progression-free survival (independent review committee; IRC) • Overall survival • Safety endpoints and Patient-reported outcomes

ERG comment:

- Well conducted and provides high quality evidence
- ALEX *'closely matches the decision problem… in the NICE final scope'*

ALEX: study design



- ALEX did not have protocol-defined crossover
- However, some sites in countries where study treatments already available → some patients switched treatments after discontinuing study treatment
- Crizotinib → alectinib = 10 patients; alectinib → crizotinib = 9 patients

ALEX: key baseline characteristics

Baseline intention-to-treat population		Alectinib (n=152)	Crizotinib (n=151)
Age	Mean (range)	56.3 (25–88)	53.8 (18–91)
Gender	Male, n (%)	68 (45)	64 (42)
Race	Asian, n (%)	69 (45)	69 (46)
	Non-Asian, n (%)	83 (55)	82 (54)
ECOG PS	0 or 1, n (%)	142 (93)	141 (93)
	2, n (%)	10 (7)	10 (7)
CNS metastases	IRC, n (%)	64 (42)	58 (38)
Stage of disease	IIIB, n (%)	4 (3)	6 (4)
	IV, n (%)	148 (97)	145 (96)
Prior brain radiation, n (%)		26 (17)	21 (14)
CNS metastases treatment	Brain surgery, n (%)	1 (4)	1 (5)
	Radiosurgery, n (%)	5 (19)	4 (18)
	WBRT, n (%)	17 (63)	16 (73)
	Other, n (%)	4 (15)	1 (5)

ERG comment on trial conduct

- In general, ALEX well conducted and provides high quality evidence
- Open-label study design → ERG prefer IRC measurements to investigator as likely to be less biased
- ALEX population younger with ↑ proportion women & non-smokers compared with wider lung cancer population → characteristic of ALK+ NSCLC population
- ALEX had ↓ proportion ECOG PS 2 than UK population in both treatment arms → ALEX population may be healthier than population eligible for alectinib if approved
- Alectinib arm may have had slightly worse prognosis at baseline than crizotinib (older, ↑ baseline brain metastases, ↑ ECOG PS 1 vs 0); however, no statistical comparisons presented
- Only 1% of patients from UK centres
- Baseline characteristics are reflective of UK population, but subsequent treatment distributions may differ according to country

Progression events in ALEX

- 1 independent committee (IRC #1) reviewed systemic events with RECIST
- Separate committee (IRC #2) assessed inter-cranial CNS progression events using CNS-RECIST criteria
- Investigators assessed progression using RECIST and brain imaging
- Progression events: systemic progression, symptomatic CNS progression & asymptomatic CNS progression (investigator assessed only)
- During clarification process, company restructured model to better demonstrate role of alectinib in CNS progression → adapted their progression-free survival to incorporate CNS events
- Progression-free survival = survival without any progression events
- CNS-progression-free survival = survival without a CNS progression event
- PFS and CNS-PFS need to be based on same measurement of events to ensure internal consistency of the economic model

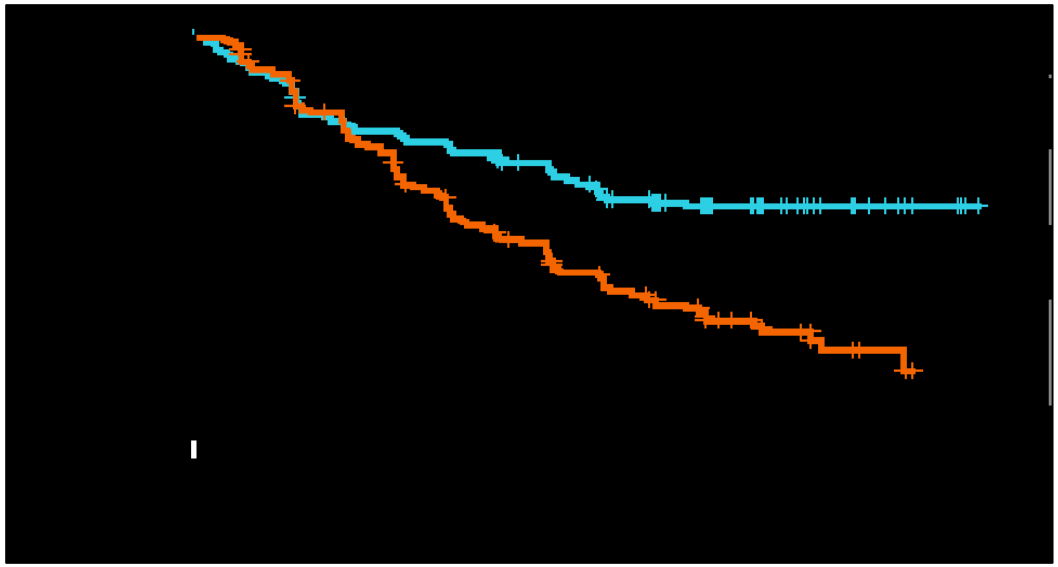
*CNS, central nervous system; INV, investigator; IRC, independent review committee; PFS, progression-free survival; RECIST, Response Evaluation Criteria In Solid Tumors)

Progression events in ALEX

- Options for analysis:
- Option 1: Add CNS RECIST outcomes to PFS data, so that PFS and CNS-PFS are both assessed by CNS-RECIST and RECIST
- Option 2: Use RECIST data as the only measure of CNS outcomes, so that PFS and CNS-PFS are both assessed by RECIST only
- Company's base case based on Option 1 → *'most complete and robust analysis of the impact of CNS metastases'*

- ERG does not consider Option 1 to be a robust method:
  - CNS-RECIST not routinely used in UK clinical practice
  - CNS-RECIST & RECIST more sensitive than RECIST → may detect events earlier than clinical practice
  - Unclear how CNS-RECIST outcomes 'added' to PFS data
- ERG could not validate event data (e.g. CNS progression events identified by CNS-RECIST before being identified by RECIST) to ensure no double counting
- ERG's preferred Option 2 (PFS and CNS-PFS based on IRC assessments using RECIST only)

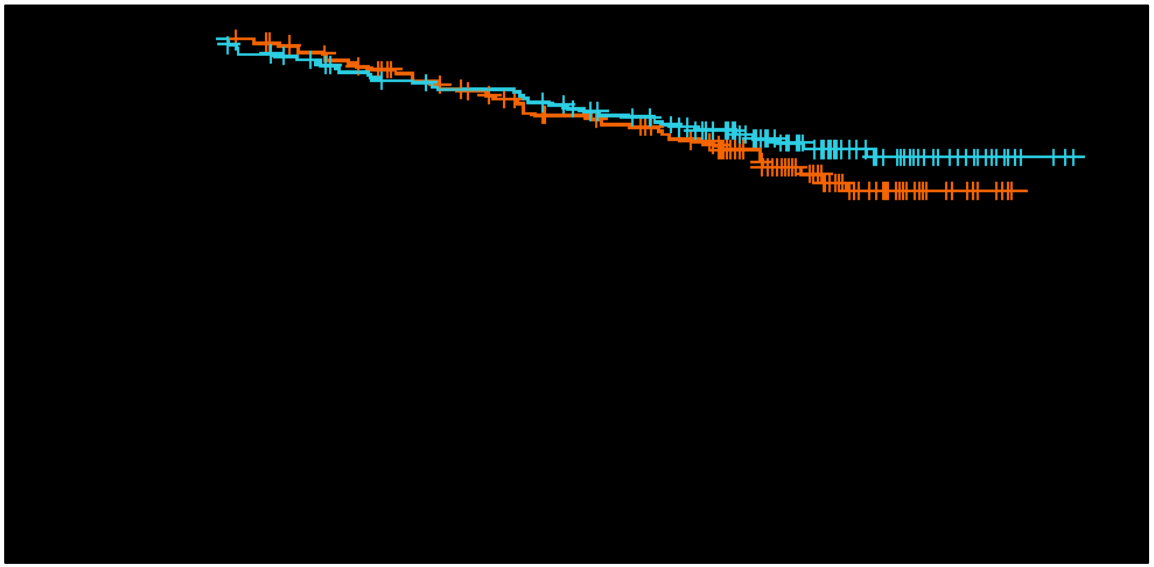
Primary outcome results: Progression-free survival (investigator)



Investigator assessed (RECIST); ITT	Alectinib n=152	Crizotinib n=151
Patients with events n (%)	62 (41)	102 (68)
Hazard ratio (95% CI)	0.47 (0.34, 0.65)	
Median duration of follow-up (months)	18.6	17.6
Median PFS (months; 95% CI)	Not met (17.7, NE)	11.1 (9.1, 13.1)
12-month event free survival (95% CI)	68.4% (61.0, 75.9)	48.7% (40.4, 56.9)

NE = not evaluable

Secondary outcome results: Overall survival



ITT	Alectinib	Crizotinib
Median duration of follow up (range)	18.6 (0.5 to 29.0)	17.6 (0.3 to 27.0)
Median overall survival (months)	NE	NE
Hazard ratio (95% confidence interval)	0.76 (0.48, 1.20)	
12-month survival rate (%; 95% confidence interval)	84.3% (78.4, 90.2)	82.5% (76.1, 88.9)

Clinical cut-off: 9th February 2017. Sample not powered to detect significant difference in OS.

Secondary outcome results: Progression-free survival (IRC: RECIST)

IRC assessed; ITT	Alectinib	Crizotinib
Hazard ratio (95% CI)	0.50 (0.36, 0.70)	
Median PFS (months; 95% CI)	25.7 (19.9, NE)	10.4 (7.7, 14.6)

- ERG's preferred measure of progression-free survival
- Prefer to investigator because of open-label study design (less open to bias)

CNS- progression-free survival

CNS-PFS = survival without any progression events in the CNS

Option 1: RECIST or CNS-RECIST

REDACTED
Commercial in confidence

Option 2: RECIST only

REDACTED
Commercial in confidence

- Patients with non-CNS progression events not censored in either CNS-PFS analysis → some of the reported CNS events included could be a second event following systemic progression ('secondary')
- ERG could not validate whether CNS events were primary or secondary
- Further uncertainty as company clarification response unclear about whether events were systematically captured after the first progression event

Secondary outcome results: Response rates & Patient reported outcomes

Response rates	IRC assessment (RECIST)	
Outcome	**Alectinib**	**Crizotinib**
Objective response rate, n (%)	120 (78.9)	109 (72.2)
Stratified OR (95% CI) [race & CNS metastases]	[redacted]	
Complete response, n (%)	[redacted]	[redacted]
Partial response, n (%)	[redacted]	[redacted]

Patient reported outcomes:

- [redacted]
- Patient-reported outcome data [redacted]
- [redacted] treatments in the time to confirmed patient- reported clinically meaningful deterioration in HRQoL [redacted]

Time-to patient reported deterioration in HRQoL: ERG *'does not consider there to be robust evidence for a meaningful difference between groups'*

Treatment beyond CNS progression

- Both IRCs were blinded and so could not assess whether CNS progression events were symptomatic or asymptomatic
- Investigators could assess whether event was asymptomatic
- If CNS progression was isolated and asymptomatic, patient could continue receiving study treatment at investigator's discretion
- However, an isolated asymptomatic CNS progression event was still considered a relevant survival event for the CNS- progression-free survival analysis

Subset of patients with progressed disease who continued to receive study treatment

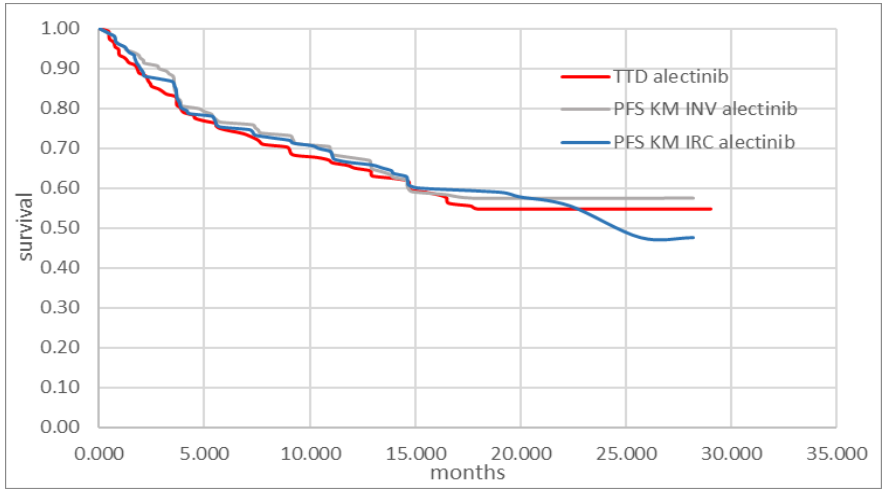
ERG comment:

- Not in marketing authorisation
- But, clinical expert advice and TA500 & TA422 indicate that UK clinical practice may be guided by symptoms rather than radiographic evidence → asymptomatic progression may not be detected in clinical practice

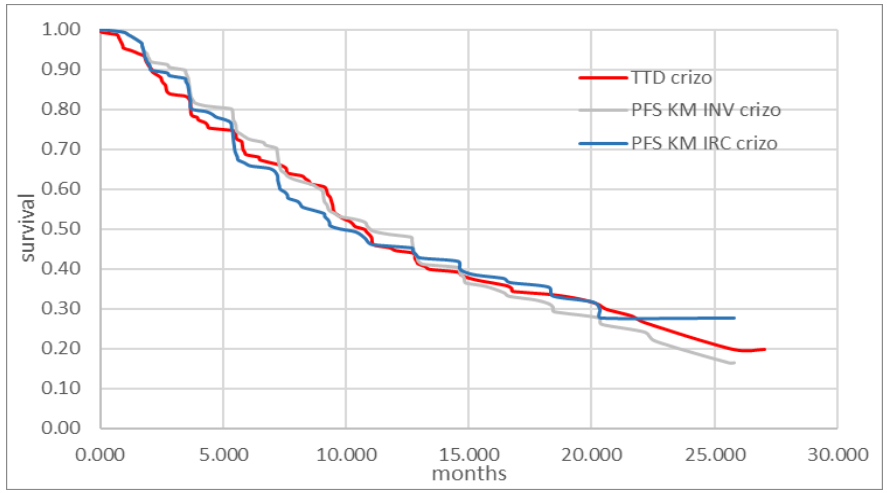
ERG comment on treatment beyond progression

- ERG compared PFS curves to time-to-discontinuation curves
- Time to progression and discontinuation similar in ALEX for both treatments
- (N.B. PFS curves only show systemic progression, not necessarily asymptomatic CNS progression)
- *'continuing treatment beyond detection of an asymptomatic, isolated CNS does not seem problematic at face value (as these patient's CNS progression would not be captured in routine clinical practice)'*

Alectinib



Crizotinib



ERG comment on subsequent treatment after progression

- Uncertainty as only 41% subsequent treatment data captured in ALEX

Alectinib:

- Uncertainty about whether clinicians would use alectinib beyond progression
- TA406 and TA500; ~75% patients received treatment beyond progression in PROFILE 1014 (crizotinib) and ASCEND-4 (ceritinib)
- Current practice = treating people with same ALK inhibitor after progression, but not covered in alectinib's marketing authorisation → uncertainty

Crizotinib:

- Bias against crizotinib if given for a shorter period in ALEX than in clinical practice (assuming that alectinib will be used according to licence)
- May also underestimate cost of treatment for crizotinib
- Disagreement from clinical experts about whether a 1st generation TKI (crizotinib) would be used after a 2nd generation TKI (alectinib)

Feedback from clinical experts

- In clinical practice, patients would switch treatment on symptomatic/ radiological progression
- People progressing on crizotinib likely to switch to a 2nd generation ALK inhibitor (ceritinib or alectinib) and then chemotherapy options → estimate ~70-80% would move from crizotinib to subsequent TKI (although Yip et al. (2017) study reported only 31% crizotinib patients receiving further ALK TKI)
- People progressing on alectinib could move to platinum doublet chemotherapy or BSC (depending on fitness) → estimate ~50% would move from alectinib to chemotherapy
- TKIs normally well tolerated. People not fit enough to receive subsequent TKI treatment would not be fit enough to receive chemotherapy
- People on alectinib would only access subsequent TKI treatments through clinical trials or compassionate access programmes

Subgroup analyses

- Alectinib performed better than crizotinib in all pre-planned subgroup analyses (baseline CNS metastases, pre-treatment radiation therapy for CNS lesions, sex, race & age) apart from 'active smokers' (HR: 1.16, 95% CI: 0.35, 3.90) and 'ECOG PS' of 2 (HR: 0.67, 95%: 0.21, 2.13)
- Overall survival in patients recorded as having subsequent anti-cancer treatment after alectinib vs patients not recorded:

	Subsequent anti-cancer tx	Not recorded
Alectinib	[redacted]	
Crizotinib	[redacted]	

- Overall survival for patients based on subsequent TKI treatment:

	Subsequent TKI	Not recorded
Alectinib	[redacted]	
Crizotinib	[redacted]	

- Company: analysis non-randomised with small sample → risk of bias
- High proportion of the 121 patients captured as 'no subsequent treatment' were still progression free and on alectinib ∴ likely to ↑ OS outcomes

All-cause adverse events

All-cause adverse events	Alectinib n=152	Crizotinib n=151
Median tx duration, months (range)	17.9 (0 to 29)	10.7 (0 to 27)
Patients with ≥1 AE, n (%)	147 (97)	146 (97)
Serious AEs, n (%)	43 (28)	44 (29)
Grade 3–5 AEs, n (%)	63 (41)	76 (50)
Fatal AEs, n (%)	5 (3)	7 (5)
AEs leading to discontinuation, n (%)	17 (11)	19 (13)
Treatment related adverse events		
Nausea (%)	7%	42%
Constipation (%)	26%	21%
Diarrhoea (%)	6%	38%
Vomiting (%)	3%	29%
Alanine aminotransferase ↑ (%)	13%	29%
Asparatate aminotransferase ↑ (%)	14%	22%
Peripheral oedema (%)	9%	23%

ERG comment: Safety assessments not blinded → potential attribution bias (particularly in treatment related events)

ERG comment on clinical evidence

- ERG's preferred PFS analysis (IRC RECIST) shows significant benefit of alectinib over crizotinib → median PFS = 25.7 vs 10.4 months
- Alectinib PFS benefit presents across majority of subgroups (except active smokers & ECOG PS 2; small sample sizes)
- ALEX not powered to detect differences in overall survival → median OS in alectinib vs crizotinib not reached. 35 patients in alectinib arm and 40 patients in crizotinib had died at data cut-off (HR: 0.76, 95% CI: 0.48, 1.20)
- ALEX doesn't demonstrate that alectinib PFS benefit translates to OS benefit
- Treatment related adverse events higher in crizotinib (89%) than alectinib (77%); however, open label → could be due to attribution bias
- Uncertainty with company's preferred PFS & CNS-PFS analyses (IRC RECIST & CNS-RECIST) → non-CNS progressive events censored in PFS analysis but not censored in CNS-PFS
- CNS-RECIST may not reflect clinical practice → ERG prefers RECIST only
- Challenge of treatment beyond asymptomatic CNS progression
- Subsequent therapies not captured systematically → limits ability to assess role on overall survival