NICE National Institute for Health and Care Excellence

Part 1

Brigatinib for ALK-positive advanced non-small cell lung cancer that has not been previously treated with an ALK inhibitor

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ERG: LRiG

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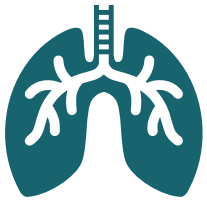
Company: Takeda

ACM 1 4th November 2020

NSCLC background: ALK+ NSCLC

Overview of NSCLC



- Lung cancer is third most common cancer in the UK (~13% of all cancer)
- Most (~ 88%) lung cancers are non-small cell lung cancer (NSCLC)
- In 2016 approximately 32,533 people were diagnosed with NSCLC in England, of whom 53% had stage IV disease
- Prognosis is often poor due to late diagnosis

ALK status

- ALK testing is a standard part of the diagnostic work-up in NSCLC
- ALK is a rare mutation with an estimated prevalence rate of between 1.6% and 5% in NSCLC, almost exclusively in adenocarcinoma NSCLCs
- ALK mutations are more common in younger people who are non-smokers
- Brain metastases are a frequent complication, occurring in 40-50% of ALK+ NSCLC

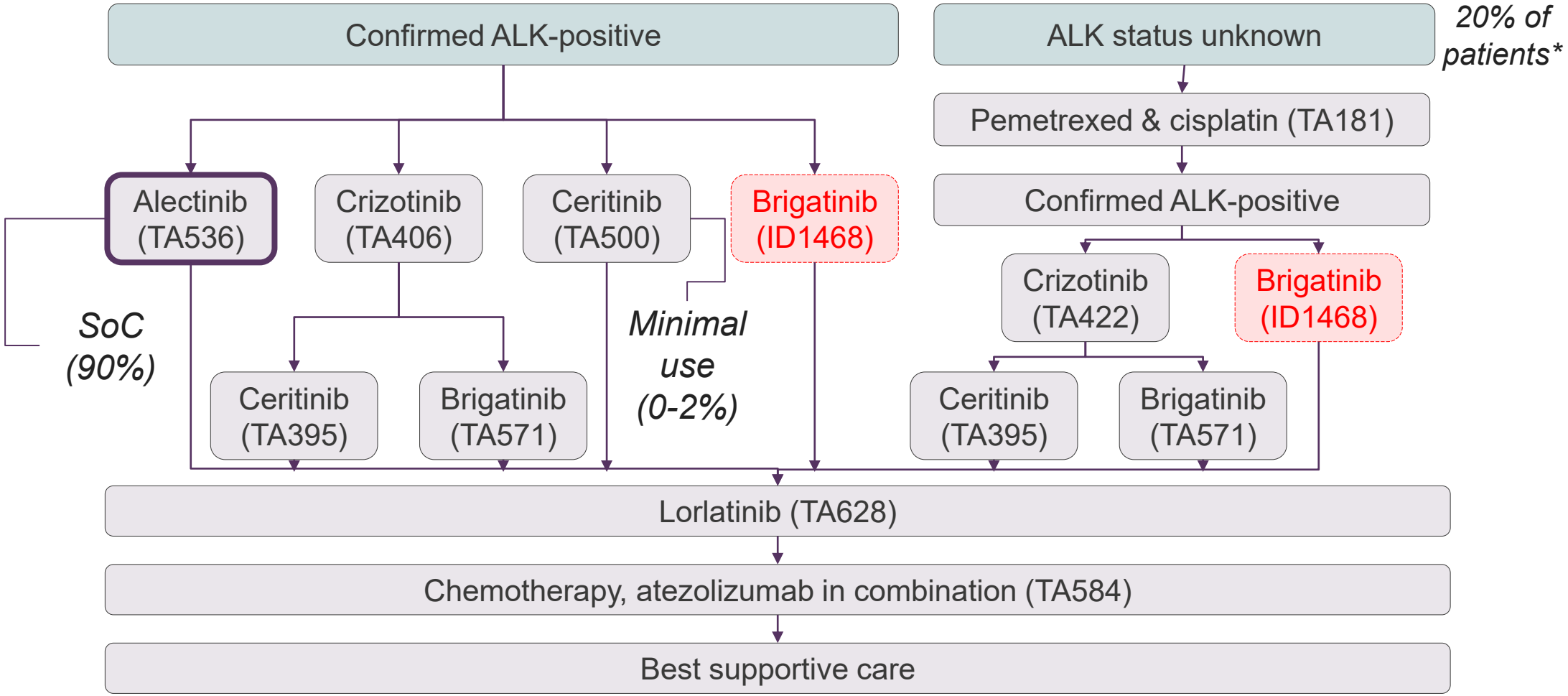
ALK = anaplastic lymphoma kinase

Brigatinib (Alunbrig, Takeda)

Marketing authorisation (received April 2020)	Monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously not treated with an ALK inhibitor
Mechanism of action	Tyrosine kinase inhibitor (TKI)
Administration, dose	Oral, 90mg once daily for the initial 7 days then, 180mg once daily
Price	List price is £4,900 applicable both to 1) starter pack (i.e. 7 tablets at 90mg + 21 tablets at 180mg) and 2) 28-tablet pack at 180mg. The mean duration of treatment is 38.34 cycles (35.27 months)
PAS	Confidential simple discount PAS has been approved

ALK = anaplastic lymphoma kinase; PAS = patient access scheme

Treatment pathway for ALK-positive NSCLC



Source: Adapted from figure 2 in company submission; ALK = anaplastic lymphoma kinase; SoC = standard of care; *Clinical expert feedback during TE TC

Patient and carer perspectives

- There are very few treatments currently available for first-line treatment of ALK-positive advanced non-small-cell lung cancer
- Many patients face a significant financial burden as a result of loss of earnings and costs associated with hospital visits such as petrol, hospital car-parking and child care
- Symptoms such as breathlessness, cough and weight loss are difficult to treat and can be distressing for loved ones to observe
- Significant impact on lifestyle including driving as the illness affects the brain and bones as well as the lungs
- Common side effects include diarrhoea, nausea, vomiting, tiredness, abdominal pain, cough, headache and decreased appetite
- Brigatinib appears to be generally well tolerated by patients

"Life changes beyond all recognition once a diagnosis has been received, not knowing how long you have to live and what quality that life will be is a dark cloud that is permanently overhead for all patients (and carers)."

Patients are diagnosed "in the prime of their lives, whilst in full time employment, with young families, about to get married, still at university…"

ALK = anaplastic lymphoma kinase

Note: Slide amended after ACM 1

Patient and carer perspectives

Advantages of brigatinib

- One tablet per day vs. 8 tablets a day for alectinib which minimises negative impact on quality of life for patients and leads to fewer visits to the doctor
- Easy to take small tablets
- Patients taking the drug do not have sun sensitivity and Brigatinib has fewer gastrointestinal side effects than alectinib
- An ALK+ UK survey of 80 patients suggested than 32% of patients who take Brigatinib have a serious adverse event versus 62% of patients treated with alectinib
- Brain coverage reduces brain metastases without need for radiotherapy

We would like to thank ALK Positive UK and the Roy Castle Lung Cancer Foundation for their submissions

Key Issues

Issue	Question for committee	Technical team	Impact
2a. ITC studies	Should the ALESIA trial be included within ITC?	Prefer inclusion of ALESIA	Small
2b. ITC methods	Are the unanchored MAIC results acceptable for use in decision-making?	Unanchored MAIC is unsuitable for decision-making	Significant
4. Cost-minimisation	Should a cost-minimisation approach versus alectinib be accepted?	There is insufficient evidence to demonstrate equivalence and accept cost-minimisation	-
6b. PD-CNS health state utility value	Is the CNS multiplier used by the company acceptable?	CNS multiplier used is not robust	Uncertain
Other	End-of-life and cancer drugs fund	-	-

Key clinical data sources

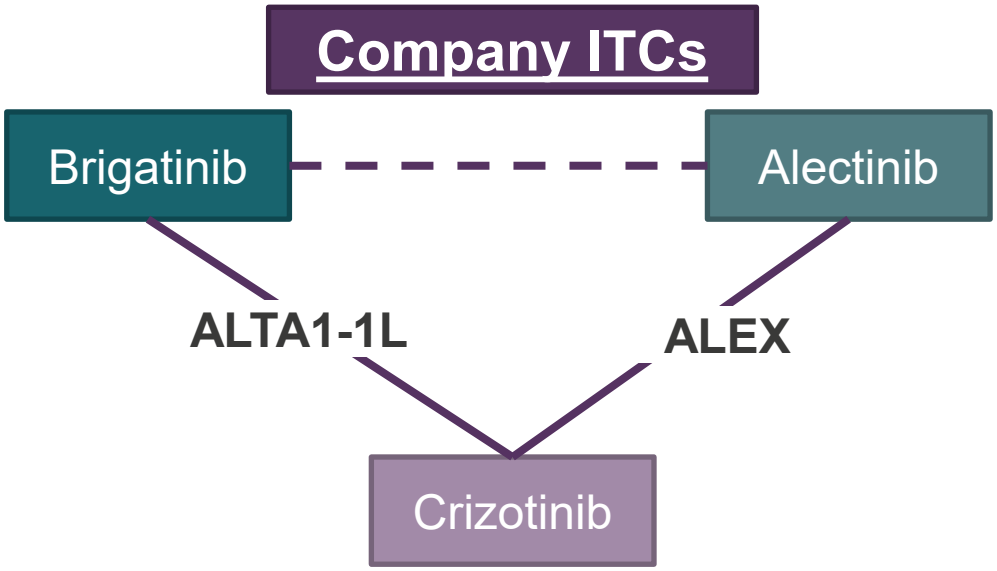
	ALTA-1L	ALEX	ALESIA
Design	Randomised, Phase 3 multi-centre, international, open-label		
Intervention	Brigatinib	Alectinib	Alectinib
Comparator	Crizotinib	Crizotinib	Crizotinib
Population	Adult patients with ALK-positive locally advanced or metastatic NSCLC who have not **been previously treated** with an ALK inhibitor	**Treatment naïve** adult patients with ALK-positive advanced NSCLC	
Primary outcome	BIRC-assessed PFS	Investigator-assessed PFS	
Included in model	Yes	Yes	**No**

Company: excluded due to being conducted in an Asian population only
ERG: exclusion is considered inappropriate and extrapolation to UK clinical practice is possible

ALK = anaplastic lymphoma kinase; BIRC = blinded independent review committee; ITC = indirect treatment comparison; PFS = progression free survival

ITC methods

An ITC using the ALTA-1L and ALEX trials was conducted because there is only 1 trial comparing brigatinib with crizotinib and no trials comparing brigatinib with alectinib



The company conducted ITCs using three methods:

- Unanchored MAIC *(company base-case)*
- Anchored MAIC
- Unweighted Bucher (as baseline reference)

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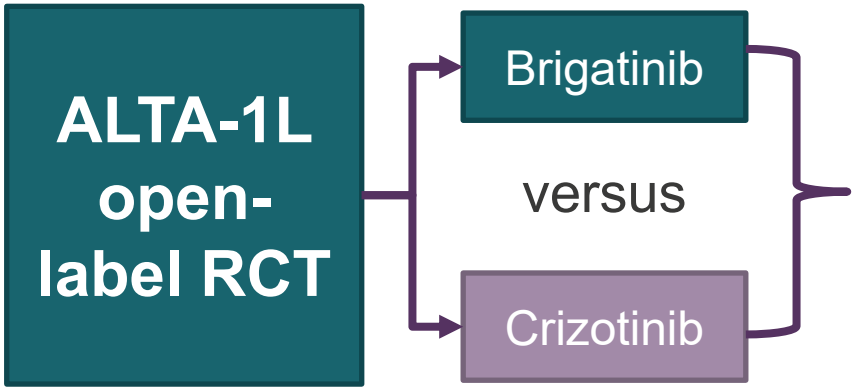
ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison

Key clinical data: ALTA-1L trial (brigatinib vs. crizotinib)



Key outcomes

- BIRC assessed PFS (primary efficacy endpoint)
- Investigator assessed PFS
- BIRC assessed intracranial PFS (to capture potential benefit in CNS)
- Overall survival (immature as median OS was not reached in either arm)

Key outcomes	Months	Hazard ratio (95% CI)
BIRC assessed median PFS	23.98 vs. 11.01	0.489 (0.35, 0.68)
Investigator assessed median PFS	29.44 vs. 9.23	0.434 (0.31, 0.61)
BIRC assessed median intracranial PFS	23.95 vs. 5.59	0.31(0.17, 0.56)
Median OS (unadjusted)	NE vs. NE	0.916 (0.57, 1.47)
OS (RPSFTM adjustment for “all switchers”, without re-censoring)*	Not reported	0.871 (0.396 to 1.789)

BIRC = blinded independent review committee; CI = confidence interval; NE = not estimable; OS = overall survival; PFS = progression free survival; RPSFTM = rank-preserving structural failure time models; *considered best available adjusted OS estimate

Key clinical data: ITCs (brigatinib vs. alectinib)

HR (95% CI)*	ALTA-1L and ALEX trials		
	Company anchored MAIC	**Company un-anchored MAIC**	**Company unweighted Bucher**
OS	1.21 (0.65 to 2.24)	0.83 (0.52 to 1.33)	1.36 (0.74 to 2.49)
BIRC PFS	0.97 (0.61 to 1.55)	0.97 (0.69 to 1.38)	1.04 (0.65 to 1.66)
Investigator PFS	0.97 (0.62 to 1.52)	0.97 (0.68 to 1.38)	1.05 (0.67 to 1.64)

Company base-case

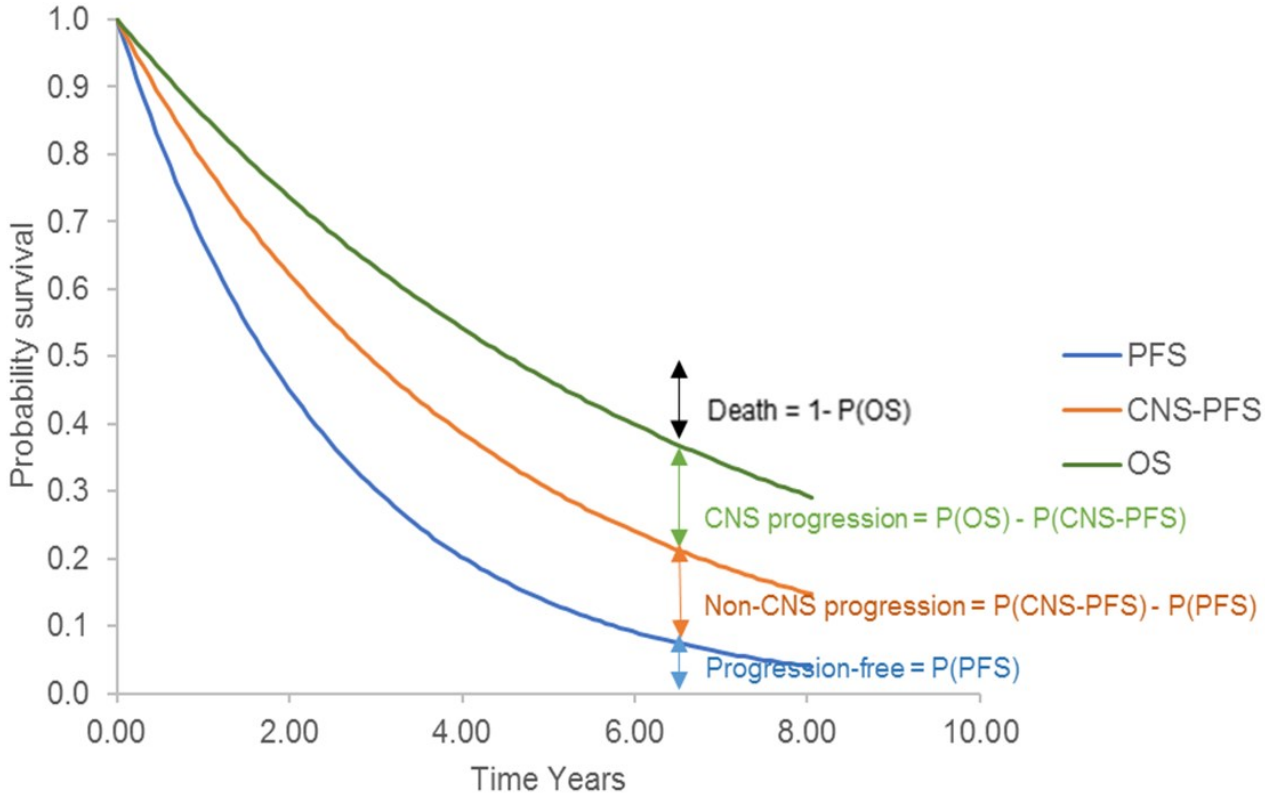
*HR<1 favours brigatinib

BIRC = Blinded independent central review; ITC = indirect treatment comparison; MAIC = matched-adjusted indirect comparison

Model background (1/2): partitioned cost-effectiveness model

Area-under-the-curve (AUC) partitioned survival analysis (PartSA) with four health-states:

- Pre-progression
- Non-CNS progression
- CNS progression
- Death



Partitioning was used to allow for consideration of the costs and HRQoL burden associated with CNS progression

 CNS = central nervous system; HRQoL = health-related quality of life

Model background (2/2): cost-minimisation compared with alectinib

The company submitted a cost-minimisation analysis because:

- Immature data led to difficulties in interpreting cost-effectiveness analysis
- Wide overlapping confidence intervals suggested similar benefit for brigatinib and alectinib
- Expert judgements from two advisory boards indicating real-world experience is similar between treatments

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Non-inferiority analyses could not be provided as:

- ALTA-1L is not designed for non-inferiority
- There are key differences between ALTA-1L and ALEX trials which could not be accounted for in a non-inferiority test
- Non-inferiority tests require a pre-specified margin based on clinical and statistical reasoning. There is no guidance on selecting this margin within NICE TSD documents

The ERG do not consider equivalence to be sufficiently demonstrated and do not consider the cost-minimisation acceptable in this appraisal

Issues resolved during technical engagement

	Summary	Stakeholder responses	Technical team	Base case?
1	**Comparator**: Company included alectinib and crizotinib as comparators. ERG consider alectinib is most appropriate	Clinical experts confirm alectinib is SoC for patients with confirmed ALK-status. Crizotinib is used in the small percentage of patients who have chemotherapy due to delayed testing	Alectinib is the primary comparator. A comparison to crizotinib is relevant for only a small portion of patients	Company X ERG ✓
5	**Duration of treatment:** Company use PFS to inform treatment duration. ERG prefer ToT	Clinical experts indicate treatment is generally continued post-progression	Use ToT to model duration of treatment	Company X ERG ✓
6a	**CNS partitioning:** Company model partitioned disease by CNS progression to account for impact of CNS involvement. ERG considered there to be insufficient evidence to partition the health state	CNS progression has a major impact on quality of life of patients, reducing independence through the loss of driving licences and increasing frequency of hospital visits	Partitioning by CNS progression is appropriate	Company ✓ ERG X

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CNS = central nervous system; PFS = progression free survival; SoC = standard of care; ToT = time on treatment

Outstanding issues after technical engagement

	Company position	Tech team preliminary judgement	Key question for committee	Impact on ICER	Slides
2	**ITC:** Unanchored MAIC, excluding ALESIA	Prefer anchored MAIC as per DSU TSD18	*Are the unanchored MAIC results acceptable for use in decision-making?*	Significant	16-18
4	**Cost-minimisation:** Comparison with alectinib can be made using a cost-minimisation approach	Insufficient data to demonstrate equivalence and accept cost-minimisation approach	*Is a cost-minimisation approach acceptable?*	-	19
6b	**PD-CNS health state utility value:** CNS multiplier based on data from Roughley et al. abstract	Data from Roughley et al. (2014) are weak	*Is the CNS multiplier used by the company acceptable?*	Uncertain	20

High priority Lower priority

DSU = Decision support unit; MAIC = matched adjusted indirect comparisons; OS = overall survival; PFS = progression free survival; TSD = Technical support document

Lower priority

Issue 2a: ITC studies

Background

ALESIA trial was conducted in Asia (China, South Korea and Thailand)

Company	Excluded ALESIA on the basis of not being representative of UK clinical practice
ERG	It is appropriate to 'extrapolate' ALESIA results and include these within ITCs: • The EPAR for brigatinib states that extrapolation in the Asian population to the European mainly white population, is possible • The ERG notes that results from the ALEX trial (which enrolled 45.8% participants from countries in Asia and only 1% of patients from the UK) were considered by the company to be relevant to the UK population

Technical engagement response

Company: ALESIA is not generalisable to England

- Less than 2% of the UK population is likely to be from China, South Korea and Thailand (ONS data)
- There may be significant regional differences in health systems and pathways of care that may impact patient outcomes

Should the ALESIA trial be included within ITC?

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EPAR = European public assessment reports; ITC = indirect treatment comparison; ONS = Office of National Statistics

High priority

Issue 2b: ITC methods

Company position	ERG position
1. Unanchored MAIC (base-case): • Estimates relative efficacy of brigatinib vs. alectinib as if they are from two single arm trials • Removes influence of treatment cross-over and differences in proportions of patients with baseline brain metastases **2. Anchored MAIC:** potentially biased by treatment switching **3. Unweighted Bucher:** included as reference. Results are similar to anchored MAIC	**1. Unanchored MAIC:** unsuitable as reliable results rely on an assumption that all prognostic factors/treatment effect modifiers are accounted for and this assumption has not been met **2. Anchored MAIC:** Best available PFS and OS estimates, however without access to IPD from the ALTA-1L trial, this cannot be replicated **3. Unweighted Bucher:** As anchored MAICs could not be conducted, the ERG has replicated unweighted Bucher ITCs

DSU TSD 18

"When connected evidence with a common comparator is available, only "anchored" forms of population adjustment may be used. "Unanchored" population adjustment may only be considered in the absence of a connected network of randomised studies, or where there are single arm studies involved."

IPD: individual patient data; ITC = indirect treatment comparison; MAIC = matched-adjusted indirect comparison

High priority

Issue 2: ITC results

HR (95% CI)*	ALTA-1L and ALEX trials				ALTA-1L, ALEX and ALESIA trials	
	Company un-anchored MAIC	**Company anchored MAIC**	**Company unweighted Bucher**	**ERG unweighted Bucher**	**ERG unweighted Bucher (FE ITC)**	**ERG unweighted Bucher (RE ITC)**
OS	0.83 (0.52 to 1.33)	1.21 (0.65 to 2.24)	1.36 (0.74 to 2.49)	1.33 (0.72 to 2.47)	1.54 (0.86 to 2.78)	1.91 (0.71 to 5.11)
Updated OS data from ALEX**	*NA: data published after company search strategy*			1.37 (0.75 to 2.51)	1.57 (0.88 to 2.82)	1.93 (0.74 to 5.02)
BIRC PFS	0.97 (0.69 to 1.38)	0.97 (0.61 to 1.55)	1.04 (0.65 to 1.66)	0.98 (0.61 to 1.57)	1.08 (0.70 to 1.66)	1.08 (0.70 to 1.66)
Investigator PFS	0.97 (0.68 to 1.38)	0.97 (0.62 to 1.52)	1.05 (0.67 to 1.64)	1.00 (0.64 to 1.54)	1.17 (0.75 to 1.81)	1.34(0.64 to 2.81)

Are the unanchored MAIC results acceptable for use in decision-making?

*HR<1 favours brigatinib; **ERG identified a paper presenting updated OS results from the ALEX trial that was published online on 11th May 2020 (outside the company's searching timeframe)

High priority

Issue 4: cost-minimisation

Company position: cost-minimisation should be the primary analysis for decision-making

- Clinical advice suggests real world efficacy is likely to be similar between brigatinib and alectinib. The wide overlapping confidence intervals (CI) in the ITCs further support this

ERG position: results should not be used to inform decision making

- Lack of statistically significant difference in company ITCs is not the same as providing statistical evidence that there is no difference between treatments
- Wide CIs can only be interpreted as a measure of uncertainty and not as evidence of similarity
- Same level of confidence in the evidence is required irrespective of whether a cost utility or cost minimisation analysis is conducted
- Failure to assess equivalence or non-inferiority before undertaking a cost minimisation analysis introduces the risk that an inferior treatment may be preferred on price alone

Technical team position: results should not be used to inform decision making

- Agree with ERG: equivalence has not been demonstrated (11 company ITCs show OS HRs of >1)

Should a cost-minimisation approach versus alectinib be accepted?

NICE CI: confidence intervals; ITC = indirect treatment comparison

Lower priority

Issue 6b: PD-CNS health state utility values

Company position: utility values for the progressed disease (PD) health state with CNS / without CNS are based on Roughley et al. 2014 abstract	
Data source *(Roughley et al. 2014)*	• Cross-sectional survey of patients with metastatic NSCLC in France and Germany • Accepted within alectinib appraisal (TA536)
EQ-5D scores	Patients with brain metastases: mean score=0.52, n=29 Patients without brain metastases: mean score=0.69, n=111
CNS multiplier	75.4% reduction in HRQoL for PD-CNS health state

ERG position

- Utility values chosen to represent PD-CNS health state are not robust. Issues with data source include:
  - Small number of patients with brain metastases
  - Treatment-related AEs, comorbidities and age were not reported
  - Limited information in abstract prevents investigation of the data reliability

Is the multiplier used for the PD-CNS health state utility value acceptable?

Note: Slide amended after ACM 1

Additional areas of uncertainty: OS data (1/2)

These are areas of uncertainty that cannot be resolved. Committee should be aware of these when making its recommendations.

Issue 3	Why issue is important	Impact on ICER
Immature overall survival evidence base	• Median overall survival in the trial has not yet been reached • The ALTA-1L trial crizotinib results are confounded by crossover and the RPFSTM adjusted OS estimates are considered unreliable by the ERG	High

- The ERG has not used alternative OS estimates for brigatinib due to markedly high uncertainty in the ITCs conducted by the company (98.6% cross-over with crizotinib in ALTA-1L)
- Of the 11 OS HRs for brigatinib versus alectinib considered by the company, only the unanchored MAIC chosen by the company resulted in a point estimate where brigatinib OS was numerically better than alectinib. The ERG considers the unanchored MAIC to be unsuitable for decision making
- Of the 10 other OS HR considered by the company, whilst the ERG considers none are robust enough to be used in favour of the unanchored MAIC, all would suggest that brigatinib would result in ICERs of over £100k compared to alectinib.

NICE RPSFTM = rank-preserving structural failure time models

Additional areas of uncertainty: OS data (2/2)

Treatment	Total life years gained	Incremental life years gained
Brigatinib	5.868	-
Crizotinib	5.610	0.26
Alectinib	5.072	0.80

- Company OS HR for brigatinib compared with alectinib is lower than OS HR used for comparison of brigatinib with crizotinib
- This results in crizotinib appearing to generate more life years than alectinib
  - This may be considered **counter-intuitive** considering that TA535 (alectinib appraisal in the same population) found alectinib to be associated with greater life years compared with crizotinib

Additional areas of uncertainty

These are areas of uncertainty that cannot be resolved. Committee should be aware of these when making its recommendations.

Issue 7	Why issue is important	Impact on ICER
Treatment waning	• **Only impacts comparison with crizotinib:** *treatment waning does not have an impact on the comparison between brigatinib with alectinib as equivalence is estimated* • Company has not waned PFS and intracranial PFS • Treatment waning for OS has been conducted at 7,10, and 20-years by the company and at 3 and 5-years by the ERG	Low

Cost-minimisation results* (brigatinib PAS only)

Note: Slide amended after ACM 1

Treatment	Total cost	Incremental costs
Brigatinib	[redacted]	N/A
Alectinib	[redacted]**	-£104,579

*Results reflect duration of treatment being calculated using PFS. Note, duration of treatment is considered to be identical for brigatinib and alectinib regardless of whether ToT or PFS is used. Differences in cost is driven by the different relative dose intensity of each product (92.76% for brigatinib and 97.8% for alectinib).

**Total cost for alectinib in the cost comparison analysis is different to the total cost for alectinib cost in the cost effectiveness analysis because the effectiveness of alectinib is equivalent to the effectiveness of brigatinib in the cost comparison analysis.

Cost-effectiveness results: brigatinib vs. alectinib (brigatinib PAS only)

Scenarios	Incremental		
	Cost	**QALYs**	**£/QALY**
A. Company base case (unanchored MAIC)	[redacted]	[redacted]	***Brigatinib dominates***
B. Corrected company base case	[redacted]	[redacted]	***Brigatinib dominates***
S1) Use of brigatinib OS estimates for crizotinib OS estimates	-	-	-
S2) Use ERG brigatinib ToT estimates to model treatment duration for brigatinib and alectinib	[redacted]	[redacted]	Brigatinib dominates
S3) Remove partitioning of PD health state	[redacted]	[redacted]	Brigatinib dominates
S4) 3-year duration of treatment effect (OS, PFS and intracranial PFS)	[redacted]	[redacted]	Brigatinib dominates
S5) 5-year duration of treatment effect (OS, PFS and intracranial PFS)	[redacted]	[redacted]	Brigatinib dominates

ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = partitioned disease; PFS = progression free survival; QALY = quality adjusted life years

Cost-effectiveness results: brigatinib vs. crizotinib (brigatinib PAS only)

Scenarios	Incremental		*ICER*
	Cost	QALYs	£/QALY
A. Company base case	[redacted]	[redacted]	***Brigatinib dominates***
B. Corrected company base case	[redacted]	[redacted]	***Brigatinib dominates***
S1) Use of brigatinib OS estimates for crizotinib OS estimates	[redacted]	[redacted]	Brigatinib dominates
S2) Use ToT to model treatment duration for brigatinib and crizotinib	[redacted]	[redacted]	Brigatinib dominates
S3) Remove partitioning of PD health state	[redacted]	[redacted]	Brigatinib dominates
S4) 3-year duration of treatment effect (OS, PFS and intracranial PFS)	[redacted]	[redacted]	Brigatinib dominates
S5) 5-year duration of treatment effect (OS, PFS and intracranial PFS)	[redacted]	[redacted]	Brigatinib dominates

ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = partitioned disease; PFS = progression free survival; QALY = quality adjusted life years

Innovation, equality and CDF

Innovation

- The company considers brigatinib to be innovative
  - The technical team considers that all relevant benefits associated with brigatinib are adequately captured in the model.

Equality

- The company submission does not identify any specific equalities considerations.

Cancer Drugs Fund

- The company submission does not include CDF proposal
- CDF should be considered if:
  - Model is structurally robust for decision-making
  - There is plausible potential to be cost-effective
  - Further data collection would reduce clinical uncertainty.