Lead team presentation
Ceritinib for untreated anaplastic lymphoma kinase-positive non-small cell lung cancer [ID1117] – STA

1st Appraisal Committee meeting

Cost effectiveness

Committee D

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ERG: CRD and CHE Technology Assessment Group, University of York

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Key cost-effectiveness issues

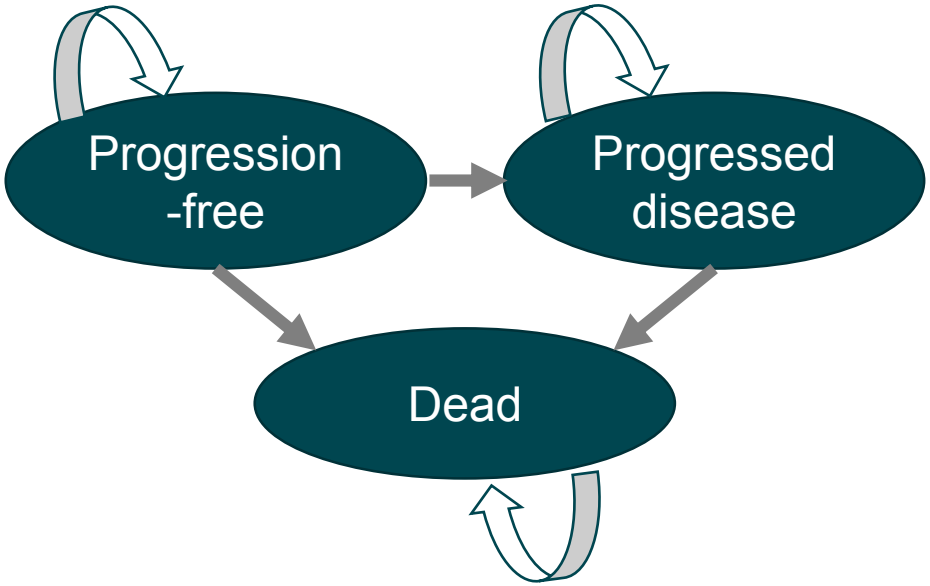
- **Survival:** In practice, what proportion of people receiving 1st line ALK inhibitor live for 5 years or more?
- **Treatment duration**: When would it be clinically appropriate to stop 1st line ALK inhibitor in practice? How long is 1st line crizotinib taken?
- **Costs**: Drug wastage? Who is responsible for monitoring and dose adjustments?
- **Utilities**: Would quality of life for someone continuing 1st line ALK inhibitor beyond RECIST-defined progression be better than someone with disease progression who switched to 2nd line treatment? Worse than someone who had a 1st line ALK inhibitor and is progression-free?

Costs and QALYs of subsequent treatment after 1st line ALK inhibitor:

  - What proportion of ALK +ve NSCLC patients in clinical practice receive active 2nd/3rd/4th line treatments? (30–40%? 60%? 80%?)
  - Should the % of people on subsequent treatments (and the distribution of treatments) reflect the trial or real world prescribing?

- **Innovation:** Is ceritinib innovative? Any benefits not captured in model?

Company model: 3-state partitioned survival model



- 20 year horizon; 2% (ceritinib) and 1% (crizotinib) patients alive at end
- 1 month cycles
- Crizotinib relative efficacy based on MAIC1 hazard ratios (PROFILE-1014)
- Costs based on trial dose intensity:
  - 77.3% ceritinib
  - 92.0% crizotinib

ERG comments

- Model structure appropriate
- Health states cannot differentiate between people on/off-treatment
- Acquisition and administration cost of ceritinib may be underestimated
- Safety not a key model driver and ERG did not explore uncertainty

Estimating PFS and OS

Company approach

	Ceritinib	Crizotinib
Base case	Parametric models fitted to ASCEND-4 patient data	Hazard ratios (HR) for crizotinib versus ceritinib (from MAIC1, using PROFILE-1014) applied to parametric models of ceritinib
Key scenarios	Data weighted to PROFILE-1014 before fitting parametric models	1 scenario applied HR from MAIC1 (as in the base case, see above)
		1 scenario fitted parametric models to *estimated* patient level data (using digitisation software)

ERG comments

- MAIC introduces substantial uncertainty in the modelled outcomes
- Proportional hazards assumption may not be supported
- Differences between trial populations might influence PFS & OS; data should be weighted to balance population characteristics

Selected parametric models

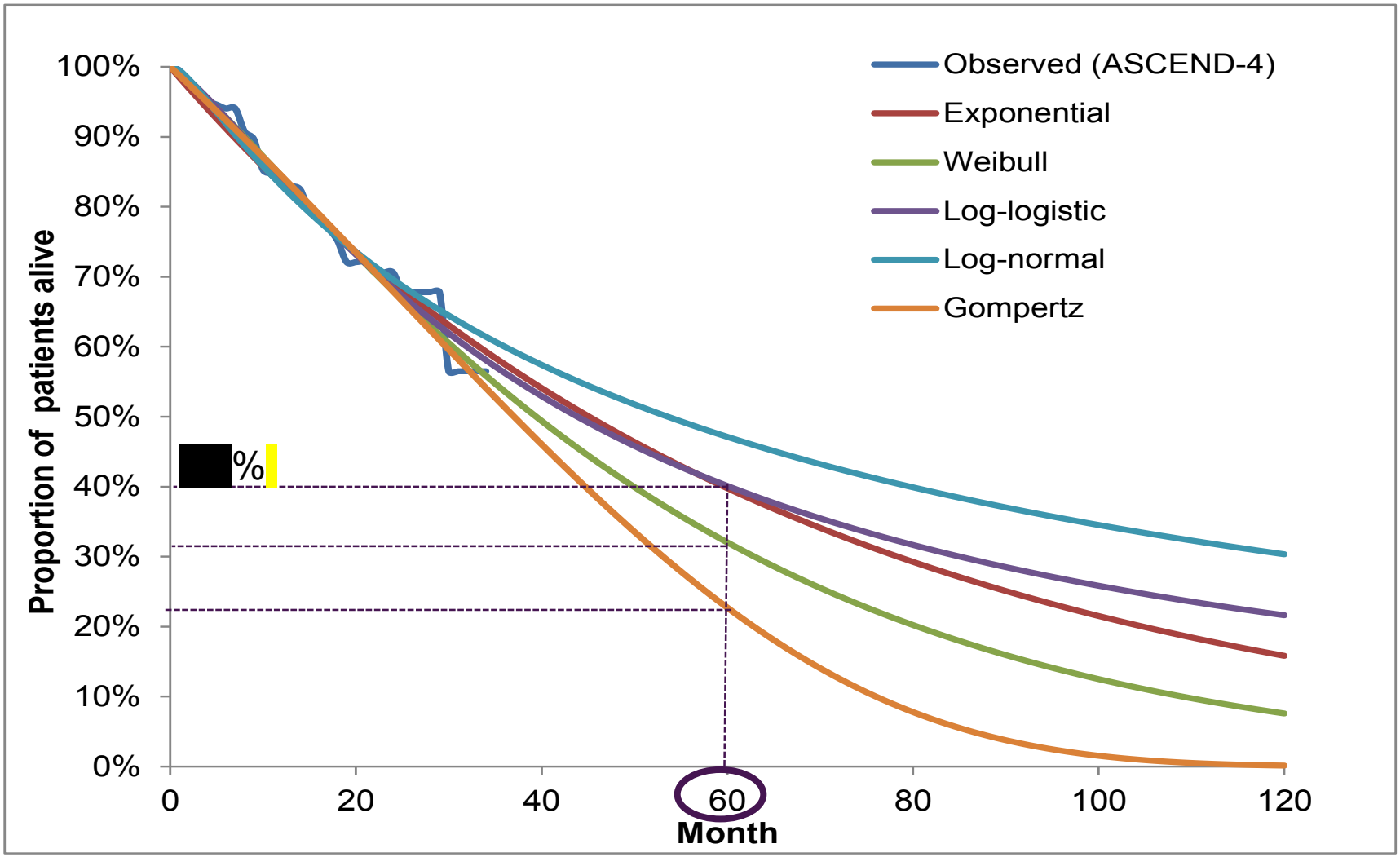
Company approach

- Exponential function for PFS and OS
- 5-year survival: [redacted]% (ceritinib) and [redacted]% (crizotinib)
- 3-year survival: [redacted]% (ceritinib) and [redacted]% (crizotinib)

ERG comments

- OS data uncertain (immature, confounded by 2nd line treatments)
- Exponential function may overestimate OS
  - clinical experts suggest 5-year survival of 20%
  - real world data (Davis 2017): 3-year survival with crizotinib [redacted]%
- Gompertz for OS (5-year survival ~20%) reflects expert advice
- Gompertz pessimistic compared with recent data from PROFILE-1014
  - 4-year survival with crizotinib of 56.6%

Observed and predicted OS for ceritinib using different parametric functions



Source: figure 18 company submission

Time on treatment (ToT)

Company base case

- Mean ToT calculated by extrapolating truncated median ToT from trials (using exponential function; individual ToT curves to model each arm)
- Mean ToT (months): [redacted] for ceritinib and [redacted] for crizotinib

ERG comments

- Model very sensitive to assumptions about ToT
- Using truncated median ToT underestimates actual ToT
  - patients in model didn't continue treatment beyond progression, which contradicts trial and practice
- Inappropriate to assume non-proportional hazards
  - inconsistent with modelling PFS
  - ToT and PFS should be modelled in same way
- Differences between trial populations might influence ToT; data should be weighted to balance population characteristics

Time on treatment (ToT)

Company scenario analysis

Ceritinib: mean ToT [redacted] months (versus [redacted] months in base case)

- Based on extrapolated patient level data (exponential function)
- Patient data from ASCEND-4 weighted to match PROFILE-1014

Crizotinib: **mean ToT [redacted] months (versus [redacted] months in base case)**

- Estimated by applying hazard ratio for crizotinib versus ceritinib [redacted] to the exponential ceritinib curve
- Hazard ratio calculated using truncated median ToT
  - 10.90 months for crizotinib (PROFILE-1014 trial)
  - [redacted] months for ceritinib (ASCEND-4 weighted to PROFILE-1014)

ERG comments

- ERG used the approach from the company's scenario analysis in its alternative base case

Costs in the progressed disease state

Company approach

- 60% of patients in each arm received second-line systemic treatment
- Second-line treatments differ in each arm
  - Base case distribution of treatments based on trial data
  - Scenario used distribution based on practice

ERG comments

- Costs and clinical data in the model are inconsistent
- 35% (ceritinib) & 43% (crizotinib) of trial patients had 2nd line treatment
- Practice: 80% of people receive subsequent treatment
- Does not account for receiving >1 subsequent active treatment
- Not appropriate to assume same duration and dose intensity for 2nd line therapy regardless of 1st line treatment because post-progression survival likely to differ in each arm
  - uncertain which arm would have longest post-progression survival

Distribution of second-line treatment according to first-line treatment arm

	Base case (based on trial)		Scenario (based on real world)	
Second-line treatment	1st line ceritinib (%)	1st line crizotinib (%)	1st line ceritinib (%)	1st line crizotinib (%)
Ceritinib	1.9	10.8	0.0	60.0
Crizotinib	9.4	1.5	0.0	0.0
Docetaxel	3.8	4.6	0.0	0.0
Platinum doublet	45.0	43.1	60.0	0.0
No active treatment	40.0	40.0	40.0	40.0

ERG comments

- Distribution in base case does not reflect clinical practice
  - for example, wouldn't have crizotinib after ceritinib
- Scenario more realistic, but inconsistent with clinical data in model

Utilities

Company approach

Health state	Utility value	Source
Ceritinib		
Progression-free	0.810	ASCEND-4
Progressed disease (PD)	0.641	Chouaid et al. 2013
Crizotinib		
Progression-free	0.810	PROFILE-1014
Progressed disease (PD)	0.641	Chouaid et al. 2013

ERG comments

- Progression-free utilities appropriate, concerns about PD utilities:
  - Inappropriate to have same utility for PD in both arms because subsequent line treatments and AEs (therefore QoL) would differ
  - Chouaid most appropriate source, but generalisability issues
  - Underestimates QoL for people with PD still on 1st line therapy
  - Method for calculating weighted average not appropriate

Summary of ERG critique

Main areas of uncertainty relate to the clinical evidence available to populate the model:

- relative treatment effect is based on the highly uncertain MAIC analysis
- hazard ratios from MAIC were applied to unadjusted survival curves from ASCEND-4 (instead of weighting data to PROFILE-1014)
- OS data are immature
- extrapolation of OS is optimistic

Also uncertainty regarding the:

- assumption of proportional hazards for PFS and OS
- methods used to estimate of duration of first-line treatment
- distribution of second-line therapies (in both treatment arms)
- duration of post-progression treatment (in both treatment arms)
- utility values in the post-progression health state
- acquisition and administration costs of ceritinib and crizotinib

ERG alternative base case

	ERG base case	Company base case
Time on treatment	Assumed proportional hazards • Ceritinib: patient-level data • Crizotinib: hazard ratio from MAIC1 (PROFILE-1014)	Used trial-derived truncated medians for both arms
Overall survival	Gompertz curve	Exponential curve
Clinical data (OS, PFS, ToT)	Adjusted ceritinib data to match PROFILE-1014 population	Unadjusted ceritinib data
% of patients on 2nd-line treatment	Based on ASCEND-4 (35%) and PROFILE-1014 (43%)	60% of patients have 2nd line treatment
	distribution of treatments was based on trials in both base cases	
Post-progression utility	• Recalculated post-progression utility • Added a health state: 'sustained utility on progression'	On-treatment post-progression utility not differentiated
Acquisition cost	Included drug wastage	Assumed no wastage
Administration cost	Additional cost for to reflect need to monitor tolerance to dose	Included only the cost of a pharmacist's time to dispense

ERG alternative base case: changes to post-progression utility

2 changes to the modelled utility values:

1. recalculated post-progression utility
2. added a health state: 'sustained utility on progression' to reflect patients who continued receiving first-line treatment beyond disease progression

Health state*	Company utility	ERG utility
Progression-free	**0.810**	**0.81**
Source	*ASCEND-4 and PROFILE-1014*	*Company base case*
Progressed disease	**0.641**	**0.56**
Source	*Weighted average from Chouaid*	*Amended weighted average from Chouaid*
Sustained utility on progression	**N/A**	**0.68**
Source	*N/A*	*Midpoint of utilities in other 2 health states*
**the same utilities were used in the ceritinib and crizotinib arm*		

Base case results (using list prices)

	Total cost, £	Total QALYs	Δ cost, £	Δ QALYs	ICER, £/QALY
Company base case					
Crizotinib	91,970	2.68			
Ceritinib	106,954	3.22	14,985	0.54	27,936
ERG alternative base case (with Gompertz OS)					
Crizotinib	119,687	2.03			
Ceritinib	139,573	2.40	19,887	0.37	53,808
ERG alternative base case (with exponential OS)					
Crizotinib	123,005	2.67			
Ceritinib	143,792	3.22	20,787	0.56	37,410

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year
Source: table 47 company submission, table 54 ERG erratum (corrected in response to issues 1, 2 and 3 of the company's factual accuracy check), table 6 ERG addendum
Results using the confidential patients access schemes for both drugs are presented in the confidential appendix to the PMB

ERG additional exploratory analyses

Additional scenarios:

- Relaxing proportional hazards assumption
  - the ERG had concerns about the robustness of these analyses
- Crizotinib outcomes based on ALEX trial (hazard ratios from MAIC2)
- Using real-world distribution of second-line treatments to calculate alternative post-progression utilities (including extra health state)
  - real-world treatment distribution resulted in different post-progression utilities in each arm (higher for crizotinib)
  - substantial increase in ICER (more QALY gains with crizotinib)
  - ERG did not favour this scenario because does not reflect clinical trial data

Innovation (comments from the company)

- Promising Innovative Medicine designation for previously treated NSCLC
- Unmet need in untreated ALK-positive NSCLC: crizotinib the only option
  - primary resistance to crizotinib in 5% of patients
  - median time to disease progression on crizotinib is 12 months
- Greater potency, specificity and penetration of blood-brain barrier than crizotinib
  - allows once daily dosing
  - translates into clinically meaningful improvement in PFS
- Benefits not captured in the QALY:
  - better tolerability than crizotinib: less grade 3/4 neutropenia and any-grade constipation, oedema and vision disorders (of these, the model costs included only grade 3/4 neutropenia)
  - reduced productivity loss, carer burden, impact on patient's family
  - psychological impact of prolonging remission and reducing number of disease progressions a patient experiences

Key clinical issues

- How reliable are results from the matched adjusted indirect comparison (MAIC)?
  - Which is more relevant: MAIC1 (PROFILE-1014) or MAIC2 (ALEX)?
  - Is PROFILE-1014 generalisable to clinical practice in the UK?
- How does the tolerability profile of ceritinib compare with crizotinib?
- Does ceritinib improve response rate and duration compared with crizotinib?

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