NICE National Institute for Health and Care Excellence

Slides for Public – ACiC Redacted

Osimertinib for treating metastatic EGFR and T790M mutation-positive non-small-cell lung cancer [ID1577]

Lead team presentation

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ERG/AG: Liverpool Reviews and Implementation Group

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Company: AstraZeneca

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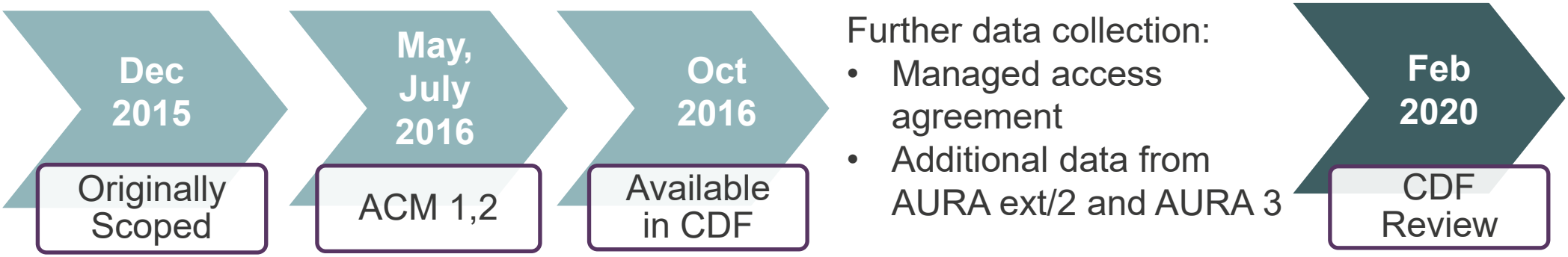
Appraisal history

Marketing Authorisation (MA): Osimertinib (Tagrisso, AstraZeneca) has a marketing authorisation for 'the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC)'. Recommended dose is 80 mg taken orally once a day until disease progression or unacceptable toxicity.

NICE TA416: *Osimertinib is recommended as an option for use within the Cancer Drugs Fund (CDF) for treating locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small-cell lung cancer (NSCLC) in adults whose disease has progressed only: after first-line treatment with an EGFR tyrosine kinase inhibitor and if the conditions in the managed access agreement for osimertinib are followed.*



Treatment pathway

First Line

Tyrosine Kinase Inhibitor afatinib, erlotinib and gefitinib

Since original appraisal:

Dacomitinib (TA 595) only if provided according to the commercial arrangement

Osimertinib (TA 621) is not recommended

Disease progression & confirmation T790M positive (non-squamous)

Second Line

Osimertinib
Access through CDF (TA416), subject of this review

Platinum Doublet Chemotherapy (PDC)

	Original scope	Original appraisal
Population	People with locally advanced or metastatic, EGFR and T790M mutation positive NSCLC	Restricted to people whose disease has progressed after first line treatment with an EGFR TKI
Comparator (based on population appraised)*	Platinum Doublet Chemotherapy (PDC)	
Outcomes	Overall survival, progression free survival, response rate, adverse treatment effects, health related quality of life	

*Scope included additional comparators for sub-populations not explored in original appraisal

Committee considerations in original appraisal

- Available evidence is for population who progressed on treatment with first line EGFR-TKI therapy
- Relevant comparator = platinum-doublet chemotherapy (PDC), including pemetrexed + carboplatin/cisplatin
- Uncertainty due to a lack of a direct comparator in clinical trials
- Likely advantage of osimertinib compared with PDC for overall response rates and progression-free survival
- Immature survival data → cannot robustly estimate relative overall survival (OS)
- Range of plausible OS extrapolations
- Most plausible utility values fall between: 0.67 and 0.831 for response, 0.67 and 0.751 for stable disease and 0.64 and 0.715 for progressed disease
- Company base-case ICER = £41,705. Committee preferred plausible ICER range = £60,663 (company preferred utilities) and £70,776 (ERG preferred utilities), based on generalised gamma OS extrapolation for osimertinib
- Uncertainty about end of life criteria → short life expectancy criterion met, uncertainty about OS gain of ≥3 months (but could plausibly meet the criteria)

New information in CDF review

Original appraisal	
AURAext/2	Pooled analysis of 2 single arm studies of osimertinib in patients with T790M positive NSCLC progressed after 1st line EGFR TKI
IMPRESS (control arm)	A subset of patients in the platinum doublet chemotherapy arm (control) retrospectively identified as T790M positive

Explored using indirect treatment comparison

CDF review	
AURAext/2	Data updated from original review
AURA3	• Randomised, open label trial in patients with T790M positive EGFRm NSCLC who progressed after 1st line EGFR-TKI • Patients randomised to osimertinib or PDC • 71% of patients randomised to PDC switched to osimertinib after disease progression
CDF SACT	Data on T790M positive NSCLC treated with osimertinib from the CDF data collection period
Non CDF SACT	• Data on patients treated with any subsequent anti-cancer treatment (not osimertinib) after initial EGFR TKI • T790M status unknown

CDF SACT data

- Eligibility criteria for technologies available through the CDF are aligned to the clinical trial to ensure real-world data is as comparable as possible

- Confidential 1-year interim SACT data or later is available for 11 technologies:
  - SACT overall survival data appears to closely align with clinical trial data or be substantially lower than clinical trial data
  - 6/11 SACT reports show similar 12-month overall survival rates
  - 5/11 SACT reports show substantially lower 12-month overall survival rates

- Real-world comparator data is not collected within the CDF

- A difference in overall survival estimates between trials and real-world evidence indicates the trials do not reflect NHS clinical practice, but does not provide any information on the real-world comparative effectiveness

Overall survival results

CONFIDENTIAL

Single-arm studies of osimertinib		
Analysis	**Results presented in TA416**	**Updated results**
	Median OS (mths) (95% CI)	**Median OS (mths) (95% CI)**
AURAext/2	Not reached	26.3 [24.02 to 29.14] (*DCO5, May 2018)*
CDF SACT	Not applicable	13.9 [12.1-17.6] *(Oct 2016-Jan 2019)*

Comparative analyses of osimertinib				
Analysis	**Results presented in TA416**		**Updated results**	
	Med OS (95% CI)	**HR (95% CI)**	**Median OS (mths) (95% CI)**	**HR (95% CI)**
AURA3*	Not applicable	----	26.8 [23.49 to 31.54] vs 22.5 [20.17 to 28.81] (DCO4, March 2019)	0.87 [0.67 to 1.13]
AURAext/2 vs IMPRESS**	Not reached vs 14.1 months	[redacted]	[redacted]	[redacted]

Other SACT Data	
Treatment	**Median OS (95% CI)**
Any 2nd line treatment***	8.31 [7.92 to 11.17]
No Treatment	2.56 [2.33 to 3.19]

*vs platinum-doublet chemotherapy, subject to71% crossover (see Issue 2)
**indirect comparison of AURAext/2 and T790M subgroup of IMPRESS placebo arm
***patients with performance status 0/1 who received any subsequent anticancer treatment

Progression-free survival results

Single-arm studies of osimertinib		
Analysis	**Results presented in TA416**	**Updated results**
	Median PFS (mths) (95% CI)	**Median PFS (mths) (95% CI)**
AURAext/2	[redacted]	----
CDF SACT	----	Not available

Comparative analyses of osimertinib				
Analysis	**Results presented in TA416**		**Updated results**	
	Median PFS (mths) (95% CI)	**Hazard Ratio (95% CI)**	**Median PFS (mths) (95% CI)**	**Hazard Ratio (95% CI)**
AURA3*	Not applicable	----	10.1 [8.3 to 12.3] vs. 4.4 [4.2 to 5.3] *(DCO1, April 2016)*	0.3 [0.23 to 4.1]
AURAext/2 vs IMPRESS**	[redacted]	[redacted]	9.7 vs 5.3	0.251, [0.155 to 0.405]

Non-CDF SACT data (Oct 2016 – Jan 2019)	
	Median PFS (95% CI)
Any 2nd line treatment***	Not available
No treatment	Not available

*vs platinum-doublet chemotherapy
**indirect comparison of AURAext/2 and T790M subgroup of IMPRESS placebo arm
***patients with performance status 0/1 who received any subsequent anticancer treatment

Patient and carer perspectives

- EGFR Positive UK, a patient organisation supporting over 100 EGFR positive lung cancer patients and their families reports that
  - Many members are younger, often never-smokers, and almost all of them were diagnosed with stage IV lung cancer
  - There are limited other options for EGFR positive NSCLC patients who develop resistance to first and second generation TKIs

EGFR Positive UK considers that osimertinib offers:

- Meaningful and significant quality of life benefit
- Significant impact of mental health and well-being of patients and their family members
- CNS control and benefit
- A daily tablet which is easy to take and cuts down on hospital appointments

Clinician perspective

- There is an unmet need for EGFR mutation positive patients who have progressed on their first line (first or second generation) EGFR TKI
- The default option is chemotherapy which has poor tolerance and clinical outcomes
- Osimertinib is well tolerated with a superior toxicity profile vs PDC
- Without access to 2nd line osimertinib overall survival of patients would almost halve and there would be an impact on their quality of life due to the burden / volume of their malignancy
- Osimertinib would be easier to use than standard of care as it is an oral medication, which patients would take at home as opposed to the alternative treatment which would be systemic anti-cancer treatment (delivered on a day unit)
- Currently we have access to osimertinib via the CDF and it would continue to be utilised as per the CDF

Key issues

Six key issues were identified during technical engagement

Issue	Description	Resolved or updated post-engagement?
1	Difference in OS estimates between trials and real world evidence	X (slides 12 to 14)
2	Treatment switching	+/- (slides 15 to 17)
3	Choice of model	✔ (slides 18 to 19)
4	Choice of OS extrapolation	✔ (slides 20 to 21)
5	Choice of utility values	+/- (slides 22 to 24)
6	End of life criteria	✔ (slides 25)

Issue 1: Differences in overall survival estimates between trials and real world evidence (1)

TA416

- Clinical effectiveness evidence taken from single arm AURA extension and AURA 2 studies for osimertinib and the IMPRESS study for platinum doublet chemotherapy (PDC)
- Committee considered data were too immature to estimate relative OS with any certainty

CDF review

- Includes updated AURAext/2data, new data from AURA 3 trial and Systemic Anti-Cancer Therapy (SACT) data on osimertinib from the CDF data collection period
- Both AURA 3 and SACT data suggest possible OS benefit of osimertinib compared with PDC
- However, median OS for osimertinib from CDF SACT data is lower than in AURA trials
- Company consider mature data from AURAext/2 resolves some uncertainty around OS benefit and estimates are in agreement with AURA 3 results
- ERG agreed that AURA3 results support findings from the AURAext/2 estimates but highlight concerns with the crossover adjustment methods (see Issue 2) and the possible impact on generalisability of results from the three AURA trials to NHS clinical practice

Median OS (mths) for osimertinib	AURAext/2	AURAext/2 & IMPRESS ITC	AURA3	CDF SACT
	26.3	*****	26.8	13.9

Issue 1: Differences in overall survival estimates between trials and real world evidence (2)

Judgement in draft technical report

AURA 3 indicates a potential survival benefit of osimertinib compared with PDC*, however note that the results were [redacted]

- Cannot conclude whether the results from AURA 3 or SACT more accurately reflect clinical reality

Company response to engagement:

- Estimates of median overall survival are consistent across studies [redacted] months for osimertinib compared with [redacted] months for PDC
- Adjusted OS hazard ratios for both studies are also consistent:
  - AURAext/2 – IMPRESS MAIC = [redacted]
  - AURA3 RPSFTM = [redacted]
- Suggests AURA3 and AURAext/2 results are aligned and reproducible in a clinical trial setting

Median time on treatment for osimertinib in both trial settings and whilst available in the CDF are very similar (AURA3; median TTD [redacted], CDF SACT; 9 months (95% CI: 8.3, 10.1)

- Reasons for difference in survival estimates include:
  - NHS patients are not as fit as trial patients and have a poorer prognosis (6% of CDF SACT patients in AURA3 had ECOG performance status of 2 and for 9% the information was missing)
  - Possible differences in post-progression care as in clinical practice patients are unlikely to receive more than 2 or 3 total lines of therapy (i.e. 1 line of therapy after osimertinib or PDC), whereas trial populations often have multiple lines of therapies after the controlled phase

**Judgement in draft technical report related to ITT analysis*

Issue 1: Differences in overall survival estimates between trials and real world evidence (3)

NCRI-ACP-RCP-RCR response to engagement:

- Overall survival (OS) was a secondary endpoint for AURA3, and the OS data is not yet mature

ERG comment on engagement responses:
The ERG agrees with the company that the PFS results from the AURA3 trial support the PFS results from the AURAext/2 and IMPRESS MAIC. However, the ERG highlights that the PDC median OS estimates from the AURA3 trial, after adjusting for crossover, range from ***** to *****and ********** median OS PDC estimates from the AURA3 trial are similar to the median OS PDC estimate from the MAIC of AURAext/2 and the IMPRESS trial. In addition, when comparing the adjusted OS hazard ratios, from the MAIC of AURAext/2 and the IMPRESS trial and the AURA 3 trial (RPFSTM base case), it is difficult to ignore the very wide confidence interval around the AURA3 trial OS hazard ratio

Final technical team judgement
The technical team cannot conclude whether the results from AURA 3 or SACT more accurately reflect clinical reality

How generalisable are trial results to the NHS clinical perspective?

Issue 2: Treatment switching in AURA3 (1)

- Company report that 71% of patients randomised to PDC switched to osimertinib after confirmed progression (AURA3)
- Osimertinib is not currently recommended by NICE for use as >2nd line therapy.
- Company adjusted using Rank Preserving Structural Failure Time Model (RPSFTM), assuming treatment effect whilst on-treatment and re-censoring applied to acceleration factor → OS HR: ********** and sensitivity analyses with various assumptions about treatment effect duration and re-censoring approaches (note: RPSFTM methods preserves the statistical significance of the ITT analysis).

Treatment effect duration	Re-censoring approach	HR (95% CI)
On treatment (osimertinib treatment effect assumed to only occur whilst on treatment)	Full (re-censoring applied in the estimation of the acceleration factor and the hazard ratio)	**********
On treatment (osimertinib treatment effect assumed to only occur whilst on treatment)	None	**********
Treatment group (osimertinib treatment effect assumed to last until death/censoring)	Acceleration factor only	**********
Treatment group (osimertinib treatment effect assumed to last until death/censoring)	Full (re-censoring applied in the estimation of the acceleration factor and the hazard ratio)	**********
Treatment group (osimertinib treatment effect assumed to last until death/censoring)	None	**********

Issue 2: Treatment switching in AURA3 (2)

- ERG not aware of any adjustment method that would produce valid effectiveness results with high crossover proportions
- ERG highlight that RPSFTM method assumes same treatment effect for 'switchers' and patients randomised to the experimental arm → may not be valid when patients switch post-progression
- ERG also note that the company's adjusted median OS estimate for PDC was more optimistic than results from the company's AURA/IMPRESS ITC or from the SACT data

Judgement in draft technical report:

- High % crossover & limitations of RPSFTM methods → uncertainty
- Technical team prefer the most cautious approach given the uncertainty and the fact the SACT OS data reflecting NHS practice is much more pessimistic than the trial data

Company response to engagement:

- Estimates to be interpreted with caution due to crossover & limitations of any adjustment method
- High level of crossover in AURA3 and current restriction of osimertinib use in the NHS in 2L patients → appropriate to adjust for
- Company note that the ERG could not suggest a better method to adjust for crossover and said that the method used in the submission was "the most reasonable"

Issue 2: Treatment switching in AURA3 (3)

NCRI-ACP-RCP-RCR response to engagement:

- Crossover needs to be considered in interpreting the survival data

ERG comment on engagement responses:

- The ERG considers that it is not possible to choose a 'best' method of crossover adjustment
- Choosing the most appropriate of the six variants of the RPFSTM method is also not possible
- Despite uncertainties, AURA3 still best data source for comparative evidence

Final technical team judgement:

- The high rate of cross-over in the AURA 3 trial means adjustment may be required but it is not possible to say with any certainty which method is most appropriate.
- The company's preferred approach is used in the ERG and technical team preferred base-case
- However, this approach is still associated with substantial uncertainty.

Should crossover be adjusted for? If so, which method should be used?

Issue 3: Choice of model (1)

- The company submitted 2 models. Model A was based on updated OS data from the pooled AURAext/2 data and data from the IMPRESS study (as per TA416). Model B was based on data from AURA 3
- The ERG identified a number of key differences between model A and model B and considered a hybrid model to be more appropriate

	Company Model A	Company Model B	ERG Hybrid Model A/B
Data source for OS/PFS/TTD	AURA pooled & IMPRESS	AURA3	AURA3
PFS extrapolation	Gompertz	Weibull	Exponential
OS extrapolation	Weibull	Log-logistic	Exponential
Utilities	Same values as in TA416 model (CR/PR 0.831, SD 0.751, PD 0.715)	EQ-5D-5L data (cross-walked to EQ-5D-3L) from AURA3	Same values as in TA416 model (CR/PR 0.831, SD 0.751, PD 0.715)
Time to treatment discontinuation (TTD)	Osimertinib: AURA2 TTD data for 14.3 months, then log-logistic extrapolation	Generalised gamma extrapolation	Exponential

Judgement in draft technical report:

- The hybrid model (model A/B) is acceptable as it uses the model from TA416 (model A) with new data from AURA 3 (model B) which the technical team agrees meets the terms of engagement

Issue 3: Choice of model (2)

Company response to engagement:

- Model A: Uncertainty due to no direct comparator
- Model B: Uncertainty due to high cross-over in AURA3
- The company response to engagement included updated base-case and scenarios where OS, PFS and TTD were modelled in line with the ERG hybrid model A/B (exponential)

ERG comment on engagement responses:

- Company model A and ERG hybrid model generate quite similar results
- Company model B appears to over-estimate

Final technical team judgement:

- The hybrid model (model A/B) is acceptable as it uses the model from TA416 (model A) with new data from AURA 3 (model B) which the technical team agrees meets the terms of engagement
- Post-technical engagement, company, ERG and technical team preferred ICERs are all based on ERG's hybrid A/B model

What is the most appropriate model?

Issue 4: OS extrapolation (1)

TA416:

- Company extrapolated OS from the pooled AURAext/2 studies & IMPRESS using a Weibull distribution for both osimertinib and PDC
- ERG considered generalised gamma might be more appropriate for osimertinib but noted that no extrapolation was more valid than any other
- Committee considered extrapolation uncertain due to the immaturity of the data

CDF review:

- Company submitted Model A & Model B and ERG submitted hybrid model (Model A/B) (see Issue 3)
- Extrapolations chosen for each of the models:
  - Company Model A → Weibull distribution for the osimertinib and PDC arms (based on statistical fit and was in line with the company's approach in the original appraisal)
  - Company Model B → log-logistic distribution to extrapolate both osimertinib and PDC treatment arms (provided the best statistical fit and closest estimate to the tail of the data)
  - ERG Model A/B → exponential functions for the OS, PFS and TTD variables.
- ERG prefer to extrapolate from point where AURA3 Kaplan-Meier data becomes heavily censored

Issue 4: OS extrapolation (2)

Judgement in draft technical report:

- Extrapolating the AURA 3 survival data from the point at which the Kaplan-Meier data becomes heavily censored is appropriate
- An exponential extrapolation of OS in both treatment arms is reasonable

Company response to engagement:

- The company agree that it is reasonable to use an exponential extrapolation of overall survival in both arms of the cost-effectiveness model
- Exponential extrapolation of OS based on ERG's hybrid Model A/B used in updated company base-case

Final technical team judgement:

- As a result of technical engagement, the company and ERG appear to agree on the use of an exponential extrapolation of OS
- However, choice of extrapolation is linked to choice of model (Issue 3). Therefore, the technical team consider that committee input on preferred extrapolation is still required

Is the exponential extrapolation of the AURA3 data acceptable?

Issue 5: Choice of utility values (1)

TA416:

- Company's preferred utilities were from AURA2/IMRESS
- ERG considered the company values to be implausibly high for metastatic NSCLC whose disease has progressed after a 1L TKI and preferred the values from the LUME-lung 1 study.
- Committee considered the most plausible values are between company & ERG values.

CDF review:

- Company Model A = values from AURA2/IMPRESS (same as TA416)
- Company Model B = values from AURA3 (similar to AURA2)
- Company argue LUME-Lung 1 utilities inappropriate as:
  - values are derived from a different patient population not previously treated with an EGFR-TKI and with unknown T790M mutation status
  - patients in the LUME-lung 1 trial were treated with cytotoxic chemotherapy
  - values do not account for response rates
- ERG base-case = values from AURA2/IMPRESS
- ERG scenario = LUME-lung 1

Utility Value			
Study	**Treatment response**	**Stable disease**	**Progressed disease**
AURA2/IMPRESS	0.831	0.751 (-0.08)*	0.715 (-0.036)*
AURA 3	0.836	0.797 (-0.039)*	0.717 (-0.08)*
LUME-Lung	0.67	0.67 (0)*	0.64 (-0.03)*

*difference in utilities from previous health state

Issue 5: Choice of utility values (2)

Judgement in draft technical report:

- Utility values from the AURA 3 trial support those from AURA2 and IMPRESS
- There is uncertainty around how generalisable the results of these trials are to NHS clinical practice (see Issue 1)
- Utility values from the LUME-lung trial should be considered alongside the AURA2 and IMPRESS and AURA3 utility values

Company response to engagement

- Utility values in AURA2 and AURA3 studies are similar = indicates most plausible utility values are those observed in the trials.
- LUME-lung 1 more aligned to experience of patients receiving platinum doublet chemotherapy
- Patient and clinician feedback suggests osimertinib significantly improves quality of life compared to standard of care → utilities modelled as health states, rather than treatment specific, may bias the results of a cost effectiveness analysis against osimertinib
- The company has updated their base case using the ERG hybrid model A/B, exponential extrapolation for overall survival and treatment specific utilities from AURA2 and LUMe-Lung1 (slide 26) and include a number of additional scenario analysis (slide 28)

	Response	Stable disease	Progressed disease	Reference
Osimertinib	0.831	0.751	0.715	AURA2
PDC	0.670	0.670	0.640	LUME-LUNG1

Issue 5: Choice of utility values (3)

NCRI-ACP-RCP-RCR response to engagement:

- Compared to chemotherapy, treatment with osimertinib was associated with lower rates of severe treatment-related toxicities. In addition, patient reported outcome measures demonstrated superior symptom control and improved patient function with osimertinib

ERG comment on engagement response:

- In original appraisal committee concluded that the true utility values associated with the pre-progression and post-progression health states were likely to lie somewhere between the estimates from the AURA2 trial and the LUME-Lung 1 trial
- The estimates from the AURA3 trial are similar to those from the AURA2 trial
- The ERG has been unable to find any utility estimates, that have been published since the original appraisal, that are relevant to patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC

Final technical team judgement:

- There remains uncertainty around the choice of utility values
- It is possible that no single utility value exists and a range of values should be considered

What are the most appropriate utility values?

Issue 6: End of life criteria

TA416

- Short life expectancy criteria was met but uncertainty around the life extension criteria
- The committee concluded that it was plausible that osimertinib met the criteria to be considered a life extending, end of life treatment

CDF review

- Point estimates from both AURA 3 and updated indirect comparison of AURAext/2 and IMPRESS indicate an overall survival gain of more than 3 months for osimertinib compared with PDC

Judgement in draft technical report:

- Point estimates from AURA 3 suggest that the life extension criteria are met, but there is substantial uncertainty about the generalisability and robustness of the trial estimates (see Issues 1 and 2)

Company response to technical engagement:

- Survival benefit in patients with T790M mutation likely to be considerably more than 3 months

ERG comment on engagement response:

Treatment with osimertinib meets both the short life expectancy and the life extension criteria

Final technical team judgement:

- Point estimates from AURA 3 suggest that the life extension criteria are met
- Uncertainty remains around the generalisability of trial estimates

Does osimertinib increase survival by ≥3 months vs PDC?

Company base-case assumptions

Base-case updated post- technical engagement

Hybrid model A/B			
Data Source for OS, PFS and TTD	AURA3		
OS extrapolation	Exponential		
PFS extrapolation	Exponential		
TTD extrapolation	Exponential		
Utilities		Osimertinib (AURA2/IMPRESS)	PDC (Lume-Lung)
	Response	0.831	0.67
	Stable disease	0.751	0.67
	Progressed disease	0.715	0.64
Commercial arrangement applied	Yes		

	Total Costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER
Osimertinib	£87,585	2.115	£66,011	1.041	£63,419
PDC	£21,575	1.075	-	-	-

ERG cost-effectiveness results
(Including commercial arrangements)

ERG base case assumptions:

- AURA 3 data used for overall survival (OS), progression free survival (PFS) and time to treatment discontinuation (TTD)
- Exponential extrapolation for OS, PFS and TTD
- Consideration of:
  - AURA2/IMPRESS utility values from TA416 (PFS: 0.831, SD: 0.751, PD: 0.715)
  - LUME-lung utilities used (PFS: 0.67, SD: 0.67, PD: 0.64)

ERG Base Case with TA416 utility values

	Total Costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER
Osimertinib	£87,585	2.115	£66,011	0.897	£73,565
PDC	£21,575	1.218	-	-	-

ERG Base Case with LUME-lung 1 utilities

	Total Costs	Total QALYs	Inc. Costs	Inc. QALYs	ICER
Osimertinib	£87,585	1.830	£66,011	0.755	£87,380
PDC	£21,575	1.075			

Utility values sensitivity analysis

Scenarios based on alternative model choices:	
Company Model A + AURA2 utility values (CR/PR: 0.831, SD: 0.751, PD: 0.715)	£68,015
Company Model A + LUME lung utility values (CR/PR: 0.67, SD: 0.67, PD: 0.64)	£79,895
Company Model B + AURA3 utility values (CR/PR: 0.836, SD: 0.797, PD: 0.717)	£88,877
Company Model B + LUME lung utility values (CR/PR: 0.67, SD: 0.67, PD: 0.64)	£104,536
New company base-case (response to technical engagement):	**ICER**
Treatment specific utilities: PDC = LUME-Lung 1 (CR/PR: 0.67, SD: 0.67, PD: 0.64) Osimertinib = AURA 2 (CR/PR: 0.831, SD: 0.751, PD: 0.715)	£63,419
Additional company scenarios (response to technical engagement):	**ICER**
Health State utilities: Midpoint between LUME-Lung 1 and AURA 2 (CR/PR: 0.751, SD: 0.711, PD:, 0.678)	£79,880
Treatment specific utilities: PDC = LUME-Lung 1 (CR/PR: 0.67, SD: 0.67, PD: 0.64) Osimertinib = Midpoint between LUME-Lung 1 and AURA 2 (CR/PR: 0.751, SD: 0.711, PD:, 0.678)	£73,496

ERG comment: The ERG has been able to replicate the ICERs generated by the additional scenarios presented in the supporting document supplied by the company. The ERG highlights that the AURA3 utility values used in these scenarios differ to those used in the company model B base case analysis.

Additional issues

Issue	Comments
Stopping treatment	• Marketing authorisation: treatment to continue until disease progression or unacceptable toxicity • AURA 3: patients can receive trial treatment after disease progression if they were receiving clinical benefit (according to investigator) • Unclear how many patients this applied to
Progression-free survival	Progression free survival (PFS) • AURA 3 → 10.1 [95% CI: 8.3 to 12.3] vs. 4.4 [95% CI 4.2 to 5.3], HR=0.3 [95% CI, 0.23 to 4.1] • CDF/SACT data → not available • AURAext/2 vs IMPRESS indirect treatment comparison → not updated
Time to treatment discontinuation	• TA416 → Time to treatment discontinuation (TTD) included appropriately • Model A → log-logistic for osimertinib; PFS estimates for PDC • Model B → generalised gamma distributions were used to estimate TTD for osimertinib and PDC separately • Model A/B → extrapolated TTD using an exponential function
Innovation	TA416 → osimertinib is innovative (no treatments for people with EGFR T790M mutation positive NSCLC resistant TKI agents so there is an unmet need) CDF Review → No additional benefits associated with this treatment that could not be captured in the economic analysis
Equality considerations	No equalities issues were identified by the company, consultees and their nominated clinical experts and patient experts

Key issues

- **Difference between trial and real world survival estimates:** How generalisable are trial results to the NHS clinical perspective? [Issue 1]
- **Treatment switching:** Should crossover be adjusted for? If so, which method should be used? [Issue 2]
- **Choice of model:** What is the most appropriate model? [Issue 3]
- **Choice of extrapolation:** Is exponential extrapolation of AURA3 data acceptable? [Issue 4]
- **Choice of utilities:** What are the most appropriate utility values? [Issue 5]
- **End of life:** Does osimertinib meet criteria to be considered a life extending, end of life treatment? [Issue 6]