NICE National Institute for Health and Care Excellence

PART 1 – slides redacted

Osimertinib for untreated EGFR mutation positive non-small cell lung cancer [ID3786]

Rapid review of TA621

Chair's presentation

ERG: Liverpool Reviews and Implementation Group (LRiG)

Technical team: Gary McVeigh, Thomas Paling, Nicola Hay, Linda Landells

Company: AstraZeneca

5 August 2020

Appraisal history: Rapid review of TA621

ACM1

- March 2019
- FLAURA suggested a survival benefit for osimertinib
- Osimertinib did not meet end-of-life (EOL) criteria
- Most plausible ICER >£30,000/QALY

ACD
Osimertinib not recommended

ACM2

- May 2019
- FLAURA subgroup analyses provided to reflect the NHS population
- Osimertinib did not meet EOL criteria
- Most plausible ICER was >£30,000/QALY

FAD TA621
Osimertinib not recommended

Appeal

- November 2019
- AstraZeneca's points considered under ground 2: "Recommendations are unreasonable in light of the evidence presented"
- Appeal upheld on the grounds that the committee considered evidence in another appraisal as relevant to this appraisal

ACM3

- January 2020
- Committee reconsidered their recommendation, "…taking care to exclude any information relating to the appraisal of dacomitinib (or any other product) from their minds"

FAD unchanged
Osimertinib not recommended

NOW

- August 2020
- Rapid review of TA621 recommendations
- Updated commercial access agreement (CAA)

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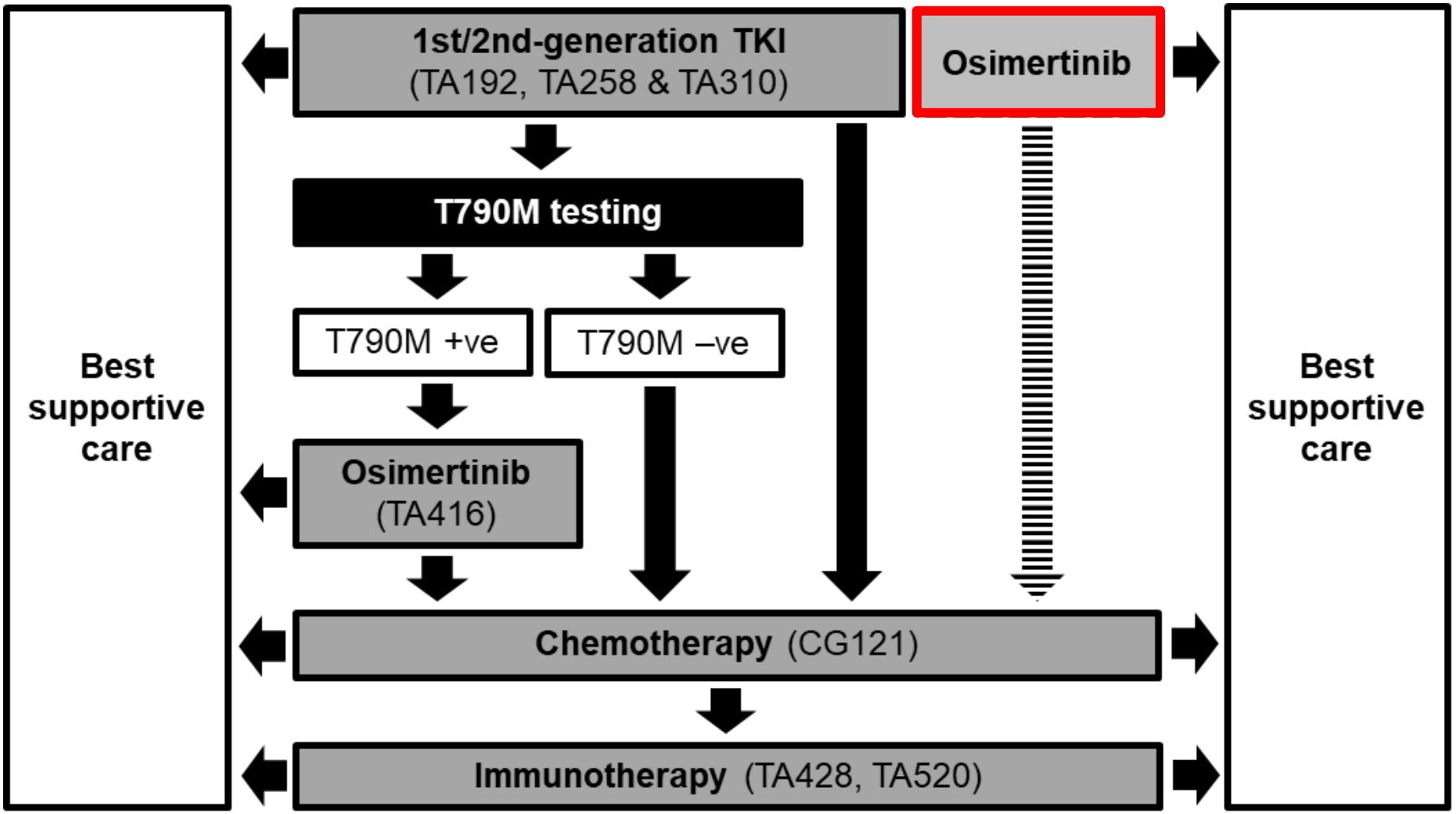
Osimertinib (Tagrisso, AstraZeneca)

Description of technology	Small molecule that selectively and irreversibly inhibits both the activating sensitising EGFR mutation (EGFRm+) and activating resistance mutation T790M, without affecting the activity of wild type EGFR. Blocking the cells ability to divide leads to tumour growth inhibition by stopping the cells from reproducing.
Marketing authorisation	Osimertinib is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) mutations. *Also indicated for:* The treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.
Dosage and administration	Oral tablet with a recommended dose of 80 mg once a day until disease progression or unacceptable toxicity.

Treatment pathway

Positioning of osimertinib in the untreated EGFR +ve setting



Source: Figure 15 TA621 company submission

Note: TA192 = Gefitinib, TA258 = Erlotinib and TA310 = Afatinib
CG121 = Lung cancer diagnosis and management,
TA428 = Pembrolizumab for PD-L1 positive
TA520 = Atezolizumab

Background: TA621

- Osimertinib is **not recommended**, within its marketing authorisation, for untreated locally advanced or metastatic epidermal growth factor receptor (EGFR) mutation-positive non-small-cell lung cancer (NSCLC) in adults.
  - Osimertinib extends progression-free and overall survival compared with gefitinib and erlotinib but the size of the benefit is unclear
  - Improved progression-free survival with afatinib compared with gefitinib → erlotinib and gefitinib cannot be assumed to have equal efficacy with afatinib
  - 6-year duration of treatment effect for osimertinib is optimistic → 3- or 5-year duration of treatment effect is more appropriate
  - Osimertinib did not meet end-of-life criteria
  - Some uncertainty could be addressed by data collection, but at the current price osimertinib does not have the potential to be cost effective* → CDF not suitable
  - Most plausible ICER was >£30,000/QALY

**The company now has an updated commercial access agreement (CAA)*

Background: TA621

NHSE comment on osimertinib

Issues and benefits may not have been captured in the economic model

- Beneficial impact of osimertinib in the brain unlikely to have been fully realised
- 1st line osimertinib will remove need for repeat bronchoscopic biopsies
- Osimertinib is better tolerated so fewer dermatology referrals needed
- Higher incidence of chronic grade 1 and 2 cutaneous toxicities associated with current 1st line EGFR-TKIs
- Because of crossover in FLAURA, the full benefit of osimertinib may not have been captured

Background TA621: duration of treatment effect

Company submission	• Company original base-case assumes 20-year treatment effect duration
Technical engagement	• Clinical expert advice indicated that treatment effect duration of up to 5 years is realistic • Previous NSCLC appraisals assumed 3-5 year treatment effect duration • Company revised base case assumes a 6-year duration of treatment effect
ACM1 → ACD/FAD	
Committee considerations	• Agreed a 6-year duration of treatment effect is overly optimistic • Acknowledged immunotherapies for NSCLC had a different mechanism of action to osimertinib and maximum treatment duration → not suitable to compare
Clinical experts	• Osimertinib is associated with improved PFS and duration of response → benefits would continue after symptomatic and radiological progression for some • Osimertinib better penetrates the blood-brain barrier → 3 months additional benefit after stopping treatment (compared with erlotinib and gefitinib) plausible
ERG	• ERG's preferred analyses used durations of 3- and 5-years • Highlighted limitations in modelling duration of treatment effect in partitioned survival model
Committee conclusions	*"… a 6-year duration of treatment effect for osimertinib was optimistic and that without more evidence, the ERG's analyses using a 3- or 5-year duration of treatment effect were more appropriate."*

Background: TA621 time to discontinuation

Model predictions: osimertinib discontinuation

	Exponential	Weibull	Gompertz	Log-logistic	Log-normal	Generalised gamma	Generalised gamma (PFS)
Mean	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 6 months	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 1 year	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 2 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 3 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
% at 4 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: table 64 original company submission

Rapid review: company submission

- PAS submission including analyses incorporating the committee's preferred assumptions from TA621 and an updated osimertinib CAA
  - [redacted]
- Analyses presented comparing osimertinib with gefitinib
  - *Gefitinib PAS is known to the company → afatinib and erlotinib are available in the NHS with confidential discounts not known to AZ*

cPAS analyses compared with afatinib and erlotinib provided by the ERG

The company's presented analyses incorporating	
Committee preferred assumptions from TA621	• Weibull extrapolation of overall survival • Progressed disease health state utility value: 0.678 • Treatment effect duration of 3- or 5-years
PAS discounts	• **Osimertinib:** revised Commercial Access Agreement (CAA) agreed with NHS England • **Gefitinib:** complex PAS, single fixed cost of £12,200 per patient irrespective of the duration of treatment [TA192]

Features of the company's economic analysis

Feature	Economic scenarios presented in this Addendum
Primary data source	FLAURA
Population	FLAURA ITT – EGFR+ NSCLC patients
Intervention	Osimertinib
Comparator	Gefitinib
Time horizon	20 years
Discount rate	3.5%
PFS extrapolation	Generalised gamma dependent extrapolation
OS extrapolation	Weibull piecewise extrapolation
Time on treatment	Mean of 23.4 months
OS Treatment effect duration	Scenario 1: 3 year treatment effect duration on OS Scenario 2: 5 years treatment effect duration on OS
Utility values	Progression-free health state utility value: 0.794 Progressed disease health state utility value: 0.678
Healthcare resource use and unit costs	Sourced from BNF, CMU, NHS reference costs, Unit Costs of Health and Social Care
Osimertinib patient access scheme	A Commercial Access Agreement has been agreed with NHS England,

NICE Source: table 1 company PAS submission

ERG review

ERG reviewed the company's PAS submission

- The company applied the following ***correctly*** in its model
  - The osimertinib commercial access agreement ([redacted])
  - Osimertinib 3-year and 5-year treatment waning effect
  - Costs of the progressed disease health state and the progressed disease utility value
- The company applied the following ***incorrectly*** in its model
  - [redacted]
  - [redacted]

ERG presented cPAS analysis for afatinib and erlotinib (considered in part 2)

- Afatinib and erlotinib are available in the NHS with confidential discounts
- ERG incorporated these prices into analyses presented in a confidential appendix

Cost effectiveness results

Company base-case

- Osimertinib CAA ***** and gefitinib PAS discounts applied
- **********

Treatment effect duration	Inc. costs	Inc. QALYs	ICER (£/QALY) vs gefitinib
Deterministic			
3 years	*****	*****	*****
5 years	*****	*****	*****
Probabilistic			
3 years	*****	*****	*****
5 years	*****	*****	*****

Source: tables 3 and 6 company PAS submission
Note: fully incremental ICERs with cPAS discounts in part 2 slides

Cost effectiveness results

ERG analysis: pairwise ICERs

ERG corrected base-case

- Afatinib and erlotinib list-prices
- Osimertinib CAA ***** and gefitinib PAS discounts applied
- **********

Treatment effect duration	Inc. costs (£)	Inc. QALYs	ICER (£/QALY)
ICERs compared with gefitinib			
3 years	*****	*****	*****
5 years	*****	*****	*****
ICERs compared with erlotinib			
3 years	*****	*****	*****
5 years	*****	*****	*****
ICERs compared with afatinib			
3 years	*****	*****	*****
5 years	*****	*****	*****

Source: tables 1-3 ERG report

Cost effectiveness results

ERG analysis: fully-incremental ICERs

ERG corrected base-case

- Afatinib and erlotinib list-prices
- Osimertinib CAA [redacted] and gefitinib PAS discounts applied
- [redacted]

Treatment	Total		Incremental		
	Costs (£)	QALYs	Costs (£)	QALYs	ICER (£/QALY)
3 year treatment effect duration					
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5 year treatment effect duration					
Gefitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Erlotinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NICE Source: tables 4-5 ERG report

Key issues

- **Treatment effect duration:** What is the likely treatment effect duration for osimertinib?
- **What is the committee's most plausible ICER?**