

**7.06 OSIMERTINIB,  
Tablet, 40mg and 80mg,  
Tagrisso<sup>®</sup>,  
AstraZeneca Pty Ltd**

**1 Purpose of Application**

- 1.1 The resubmission requested a Section 85, Authority Required listing for osimertinib for the treatment of patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC) who have progressed on or after prior treatment with an EGFR tyrosine kinase inhibitor (TKI). The first submission was considered by the PBAC in November 2017.
- 1.2 The requested listing was based on a cost-utility analyses of osimertinib compared with platinum-based doublet chemotherapy. The key components of the clinical issue addressed by the resubmission are summarised in the table below.

**Table 1: Key components of the clinical issue addressed by the resubmission**

<b>Component</b>	<b>Description</b>
Population	Locally advanced or metastatic NSCLC patients, who have progressed on or after treatment with an EGFR TKI
Intervention	EGFR mutation test to determine T790M status If T790M mutation positive, receive osimertinib
Comparator	No EGFR mutation test to determine T790M status, all patients receive platinum-based doublet chemotherapy
Outcomes	PFS, OS, ORR, DCR, tumour shrinkage, quality of life, safety and tolerability for osimertinib versus platinum-based doublet chemotherapy
Clinical claim	In patients with locally advanced or metastatic EGFR T790M mutation positive NSCLC, osimertinib is superior to platinum-based doublet chemotherapy in terms of efficacy, safety and quality of life

DCR = disease control rate; EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; TKI= tyrosine kinase inhibitor; PFS = progression-free survival.

Source: Table 1, p15 of the main body of the resubmission.

## 2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat are in italics, and deletions in strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
OSIMERTINIB 80 mg tablet, 30	1	5	\$ [REDACTED] (published) \$ [REDACTED] (effective)	Tagrisso® AstraZeneca Pty Ltd

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Locally advanced (Stage IIIB) or metastatic (Stage IV)
<b>Condition:</b>	Non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer
<b>Treatment phase:</b>	Initial <i>treatment</i>
<b>Restriction Level / Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	The treatment must be <del>as monotherapy</del> <i>the sole PBS-subsidised therapy for this condition,</i>  AND  Patient must have progressive disease following treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).
<b>Population criteria:</b>	Patient must have evidence of a T790M mutation of the EGFR gene in tumour tissue material following progression on or after an EGFR TKI.
<b>Administrative Advice</b>	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
OSIMERTINIB 40 mg tablet, 30	1	5	\$ [REDACTED] (published) \$ [REDACTED] (effective)	Tagrisso® AstraZeneca Pty Ltd
80 mg tablet, 30	1	5	\$ [REDACTED] (published) \$ [REDACTED] (effective)	

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Locally advanced (Stage IIIB) or metastatic (Stage IV)
<b>Condition:</b>	Non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer
<b>Treatment phase:</b>	Continuing <i>treatment</i>

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<b>Restriction Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone <input type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required – Electronic <input checked="" type="checkbox"/> Streamlined
<b>Clinical criteria:</b>	<p>The treatment must be as monotherapy <del>the sole</del> <i>the sole PBS-subsidised therapy for this condition,</i></p> <p>AND</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition,</p> <p>AND</p> <p>Patient must not have progressive disease following PBS-subsidised treatment with this drug for this condition.</p>
<b>Administrative Advice</b>	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
OSIMERTINIB 40 mg tablet, 30	1	5	\$ [redacted] (published) \$ [redacted] (effective)	Tagrisso® AstraZeneca Pty Ltd
80 mg tablet, 30	1	5	\$ [redacted] (published) \$ [redacted] (effective)	

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Severity:</b>	Locally advanced (Stage IIIB) or metastatic (Stage IV)
<b>Condition:</b>	Non-small cell lung cancer (NSCLC)
<b>PBS Indication:</b>	Locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer
<b>Treatment phase:</b>	Grandfathering <i>treatment</i>
<b>Restriction Method:</b>	<input type="checkbox"/> Restricted benefit <input checked="" type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required - Emergency <input checked="" type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

<b>Clinical criteria:</b>	<p>Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date],</p> <p>AND</p> <p>The treatment must be as <del>monotherapy</del> <i>the sole PBS-subsidised therapy for this condition,</i></p> <p>AND</p> <p>Patient must have progressive disease following treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).</p> <p>AND</p> <p>Patient must not have progressive disease following treatment with this drug for this condition.</p>
<b>Population criteria:</b>	Patient must have evidence of a T790M mutation of the EGFR gene in tumour tissue material following progression on or after an EGFR TKI.
<b>Prescribing Instructions</b>	A patient may qualify for PBS-subsidised treatment under this restriction once only.
<b>Administrative Advice</b>	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

- 2.2 The resubmission proposed a Special Pricing Arrangement (SPA). The proposed effective price for osimertinib represents a [REDACTED] % rebate on the published dispensed price for maximum quantity. The pre-PBAC response increased the proposed rebate from [REDACTED] % to [REDACTED] %.
- 2.3 As was the case for the previous submission, the requested listing allows patients with any performance status (PS) to receive treatment with osimertinib. This is inconsistent with the AURA3 trial, which only included patients with a World Health Organisation (WHO) PS of 0 or 1. This is also inconsistent with the restriction for other PBS listings for oral treatments for NSCLC, such as gefitinib and erlotinib, which include the clinical criterion “Patient must have a WHO performance status of 2 or less”. The PBAC advised that the criterion ‘The patients must have a WHO performance status of 2 or less’ be added to the proposed restriction to maintain alignment with the restrictions of the currently PBS-listed first line TKIs, i.e. erlotinib and gefitinib.
- 2.4 The proposed restriction does not exclude use of osimertinib after platinum-based doublet chemotherapy. This is inconsistent with the eligibility criteria of the AURA3 trial which enrolled patients with evidence of radiological disease progression, following first-line EGFR-TKI (i.e. first-line treatment for advanced/metastatic disease), without any further treatment. Patients with more than one prior line of treatment for advanced NSCLC were excluded.

For more detail on PBAC’s view, see section 7 PBAC outcome.

### 3 Background

#### **Registration status**

3.1 Osimertinib was registered by the TGA on 3 August 2016 for “the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive non-small cell lung cancer”.

#### **Previous PBAC consideration**

3.2 The November 2017 submission was an integrated co-dependent submission considered by both the Medical Services Advisory Committee (MSAC) and the PBAC in November 2017.

3.3 The November 2017 submission requested:

- Pharmaceutical Benefits Schedule (PBS) listing for osimertinib in patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation positive non-small cell lung cancer (NSCLC), who have progressed on or after treatment with an EGFR tyrosine kinase receptor (TKI); and
- Medicare Benefits Schedule (MBS) listing for EGFR T790M mutation testing in patients with locally advanced or metastatic NSCLC, to determine eligibility for access to PBS-subsidised osimertinib.

3.4 MSAC outcome (Application number 1407): MSAC deferred its advice<sup>1</sup> until such time as the PBAC subsequently decides to recommend the PBS listing of osimertinib for the requested population. MSAC foreshadowed its support for a new MBS item for EGFR T790M mutation testing in tumour tissue obtained after progression on or after therapy with a TKI to help determine eligibility for PBS-subsidised second-line osimertinib for the targeted treatment of patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC. This support is subject to a PBAC recommendation to list osimertinib once PBAC’s concerns regarding the medicines’ cost effectiveness are resolved.

3.5 The PBAC decided not to recommend a PBS listing for osimertinib in November 2017. The table below summarises the key outstanding matters from the previous PBAC considerations and how the resubmission addressed those concerns.

**Table 2: Summary of outstanding matters of concern**

<b>Component</b>	<b>Matter of concern</b>	<b>How the resubmission addresses it</b>
Requested listing	The proposed PBS restriction did not specify the type of sample to be used (tumour tissue or plasma) for T790M testing.	The requested listing in the resubmission specified that evidence of the presence of T790M should be based on a sample obtained from tumour tissue.
The claimed OS benefit of osimertinib over platinum-	[PBAC 7.7,7.8; PBAC 7.9] Because OS data from the direct AURA3 trial were immature	The resubmission presented updated OS data from AURA3 (data cut-off

<sup>1</sup> <http://www.msac.gov.au/internet/msac/publishing.nsf/Content/1407-public>

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Component	Matter of concern	How the resubmission addresses it
based doublet chemotherapy	<p>(interim analysis data-cut-off September 2016; █% maturity) and contaminated (█% of patients switched from chemotherapy to osimertinib upon progression), the submission presented a naïve indirect comparison between subgroups from single-arm studies for osimertinib (AURA Pooled [AURA1C and AURA2] and for chemotherapy (IMPRESS) to claim an OS advantage in favour of osimertinib.</p> <p>The PBAC considered this approach to be associated with a high risk of bias and that it introduces more uncertainty. The PBAC requested an ITT analysis of more mature AURA3 OS data and/or possibly a well-justified adjustment for treatment switching.</p>	<p>█; █% maturity, █% of patients switched from chemotherapy to osimertinib upon disease progression) with adjustment of treatment switching using the Rank Preserving Structural Failure time (RPSFT) model. An intention-to-treat analysis was also presented in the economic model (as a sensitivity analysis) but the RPSFT adjusted OS was used as the base case of economic model.</p>
Time horizon of the economic model	<p>[Paragraph 7.12] The PBAC considered that the submission's choice of a base case 10-year time horizon was unrealistically long and therefore implausible and overly optimistic.</p>	<p>The time horizon of the model presented in the resubmission was the same as in the previous submission (10 years). The selection of a longer time horizon was not adequately justified in the resubmission.</p>
Structure issue of the economic model	<p>[Paragraph 7.13] The PBAC agreed with the ESC that there were several structural issues with the economic model presented in the submission, including (i) confounding due to the use of OS data from single-arm studies (AURA Pooled and IMPRESS) instead of the randomised trial (AURA3) to inform the economic model; (ii) inappropriate transition probabilities and utilities; (iii) the model's assumption that only patients in the chemotherapy arm could subsequently receive nivolumab; (iv) the assumption of constant transition probabilities beyond the study period, which implied an ongoing treatment effect; and (v) the use of a non-concurrent control (OS data from the chemotherapy arm of IMPRESS) which underestimated the survival gain associated with chemotherapy, potentially biasing the model in favour of osimertinib.</p>	<p>Issues (i) and (v) have been addressed as the current economic model was based on the direct trial comparing osimertinib with platinum-doublet chemotherapy in patients with T790M mutation positive NSCLC, after progression following EGFR TKI. The ITT OS results of the direct AURA3 trial were adjusted for treatment switching from chemotherapy to osimertinib using the RPSFT model. The underlying 'common treatment effect' assumption of the RPSFT method is difficult to verify.</p> <p>All the other issues/assumptions were unchanged in the resubmission's economic model. However, the impact of changes in these inputs has been explored via a number of sensitivity analyses.</p>
Pemetrexed maintenance therapy	<p>[Paragraph 7.14] Additionally, the PBAC considered that pemetrexed maintenance was not allowed in the IMPRESS study, although the submission claimed that majority of patients (73.2%) would receive pemetrexed maintenance in Australian clinical practice. Further, while the economic model was not adjusted for this anomaly, the costs of pemetrexed maintenance were applied in the model, biasing the results in favour of osimertinib.</p>	<p>This issue has now been resolved. In AURA3, from which survival data used in the economic model were sourced, 73% of patients who completed ≥4 cycles of platinum-based doublet chemotherapy went on to receive pemetrexed maintenance monotherapy. Therefore, the survival benefits associated with pemetrexed maintenance monotherapy were implicitly captured.</p>
Cost of osimertinib per	<p>[Paragraph 7.15] The PBAC considered that the</p>	<p>The Sponsor expressed its willingness</p>

Component	Matter of concern	How the resubmission addresses it
treatment course	cost of osimertinib used in the economic model was an underestimate, as it was based on the observed truncated mean duration of treatment on osimertinib in the AURA3 study.	to enter a RSA with the Commonwealth based [REDACTED] Therefore, the risk of underestimating the osimertinib treatment duration is unlikely to be mitigated by the proposed RSA.
Extent of use of osimertinib	[Paragraph 7.16] The PBAC considered that uncertainty regarding financial implications remained in the duration of treatment in clinical practice, and a significant risk of leakage to first-line therapy, especially given that a trial of osimertinib (FLAURA) is underway in this setting.	The same financial concerns remained. The resubmission proposed a RSA to reduce the uncertainty with respect to the expenditure.

ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; RSA = Risk-sharing Arrangement  
 Source: Table constructed during the evaluation

For more detail on PBAC’s view, see section 7 PBAC outcome.

## 4 Population and disease

- 4.1 NSCLC accounts for over 80% of all lung cancer cases. Approximately 50% of patients with lung cancer are diagnosed at an advanced/inoperable stage and prognosis is poor.
- 4.2 The resubmission requested listing of osimertinib for T790M mutation positive patients who have failed first-line EGFR TKIs. T790M mutations become more common following treatment with EGFR TKIs as proliferation of EGFR T790M mutation positive clones increases in the absence of competitive pressure from tumour cells which are suppressed by EGFR TKIs. Overall, EGFR T790M mutations are detected in approximately 60%<sup>2</sup> of patients with locally advanced or metastatic NSCLC who have progressed on or after treatment with an EGFR TKI. Currently, second-line treatment most commonly consists of platinum-based doublet chemotherapy.

For more detail on PBAC’s view, see section 7 PBAC outcome.

## 5 Comparator

- 5.1 The resubmission nominated no testing for EGFR T790M mutation and all patients treated with platinum-based doublet chemotherapy as the main comparator. This was reasonable and unchanged from the previous submission.

<sup>2</sup> Wang S, Cang S, Liu D. Third-generation inhibitors targeting EGFR T790M mutation in advanced non-small cell lung cancer. J Hematol Oncol. 2016 Apr 12;9:34

For more detail on PBAC's view, see section 7 PBAC outcome.

## 6 Consideration of the evidence

### ***Sponsor hearing***

- 6.1 The sponsor requested a hearing for this item. At the hearing, the sponsor presented data highlighting the benefits of osimertinib treatment in EGFR T790M mutation positive NSCLC. The sponsor discussed the benefits of osimertinib treatment over chemotherapy, particularly in patients who had central nervous system (CNS) metastases at baseline. The sponsor discussed the merits of the various methods used to adjust for crossover in the submission, reiterated its pre-PBAC pricing proposal, and addressed other matters in response to the Committee's questions.

### ***Consumer comments***

- 6.2 The PBAC noted and welcomed the input from individuals (29), health professional (5) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described benefits of treatment with osimertinib, and emphasized its efficacy in reducing tumour burden and improving quality of life.
- 6.3 The PBAC noted the advice received from Rare Cancers Australia stating that the PBS listing of osimertinib would offer a clinically effective treatment option with very few serious side effects for EGFR mutation positive NSCLC in Australia. A comment from the Lung Foundation highlighted osimertinib's tolerability profile, compared to standard chemotherapy.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the osimertinib submission, noting that the PBS listing of osimertinib in this population would fill a significant area of unmet need. The PBAC noted that the MOGA presented the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for osimertinib, which was limited to 4 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)<sup>3</sup>, based on a comparison against platinum-based chemotherapy and pemetrexed treatment.

### ***Clinical trials***

- 6.5 The resubmission was based on a direct randomised open-label trial (AURA3) comparing osimertinib with platinum-based doublet chemotherapy in locally advanced or metastatic NSCLC patients whose disease has progressed following previous EGFR TKI therapy and whose tumours harboured a T790M mutation determined from a tumour biopsy. The key evidence in the November 2017 submission was based on a naïve indirect comparison.

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<sup>3</sup> Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

- 6.6 The November 2017 submission argued that because of the immaturity of the AURA3 overall survival (OS) data (data cut-off [DCO] September 2016; █% maturity) and the substantial proportion of patients who switched from the chemotherapy arm to osimertinib upon disease progression (█%), the AURA3 results favoured chemotherapy. Instead, the submission presented a naïve indirect comparison between subgroups from single-arm studies for osimertinib (AURA Pooled (AURA1C and AURA2)) and for chemotherapy (IMPRESS) to claim an OS advantage in favour of osimertinib.
- 6.7 The resubmission presented updated OS data from AURA3 (█; █% maturity) with adjustment of OS for treatment switching (█% switching from chemotherapy to osimertinib) using the Rank Preserving Structural Failure time (RPSTF) model. An intention-to-treat (ITT) analysis was also presented but the RPSFT adjusted OS was used as the base case of the economic model.
- 6.8 Details of the trials presented in the submission are provided in the table below.

**Table 3: Trials and associated reports presented in the resubmission**

Trial ID	Protocol title/ Publication title	Study report date/Publication citation
AURA3	<u>Internal study reports</u>	
	A Phase III, open-label, randomized study of AZD9291 (Osimertinib) versus platinum-based doublet chemotherapy for patients with locally advanced or metastatic non-small cell lung cancer whose disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy and whose tumours harbour a T790M mutation within the epidermal growth factor receptor gene (AURA3). Clinical Study Report D5160C00003. Edition 2, Data Cut-off 15 April 2016. Clinical Study Report D5160C00003. Edition 2, Data Cut-off 15 April 2016.	█
	Clinical Study Report Addendum for Osimertinib (TAGRISSO™, AZD9291) Study D5160C00003. Edition 1, Data cut-off 2 September 2016.	█
	Multi-study analysis of TAGRISSO™ (Osimertinib) efficacy in patients with central nervous system (CNS) metastases secondary to epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC).	█
	<u>Publications</u> Lee CK, Novello S, Ryden A, Templeton A, Rudell K, Mann H, Ghorghiu S, Mok T. Patient-reported symptoms and impact of treatment with osimertinib vs chemotherapy for advanced non-small cell lung cancer Mok T, Ahn MJ, Han JY, Kang JH, Katakami N, Kim HR, Hodge R, Ghorghiu DC, Cantarini M, Wu YL, Papadimitrakopoulou V, Garassino MC. CNS response to osimertinib in patients (pts) with T790M-positive advanced NSCLC: Data from a randomized phase III trial (AURA3).	Annals of Oncology 2017; 28 (Supplement 2):iii30  Journal of Clinical Oncology Conference 2017; 35(15 Supplement 1).

	<p>Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer.</p> <p>Mok TS, Wu YL, Papadimitrakopoulou VA. Osimertinib in EGFR T790M-Positive Lung Cancer.</p> <p>Papadimitrakopoulou et al. Randomized Phase III study of osimertinib vs platinum-pemetrexed for EGFR T790M-positive advanced NSCLC (AURA3).</p> <p>Sebastian M, Ryden A, Walding A, Giorghiu S, Rudell K, Papadimitrakopoulou V. Adverse events self-reported by patients with advanced non-small cell lung cancer treated with osimertinib or chemotherapy.</p> <p>Sebastian M, Schuler M, Schulz C, Deschler-Baier B, Kimmich M, Hilgert-Daute K, Griesinger F. Randomised Phase III study of osimertinib vs platinumpemetrexed for EGFR T790M-positive advanced NSCLC (AURA3).</p> <p>Wu et al (2017). Osimertinib vs platinum-pemetrexed for T790M-mutation positive advanced NSCLC (AURA3): Plasma ctDNA analysis.</p> <p>Wu Y-L, Papadimitrakopoulou V, Giorghiu S, Templeton A, Mok T. Aura3 design: a randomised, phase III study of AZD9291 versus second-line chemotherapy for patients (PTS) with EGFR-TKI-resistant (T790M) advanced non-small cell lung cancer.</p>	<p>New England Journal of Medicine 2017; 376 (7):629-640</p> <p>The New England journal of medicine. 2017;376(20):1993-4</p> <p>Journal of Thoracic Oncology 2017; 12(1):S5-S6.</p> <p>Annals of Oncology. 2017;28 (Supplement 2):iii34</p> <p>Oncology research and treatment Conference: jahrestagung der deutschen, osterreichischen und schweizerischen gesellschaften fur hamatologie und medizinische onkologie 2017; Germany; 40 (Supplement 3):p170</p> <p>Journal of Thoracic Oncology 2017;12(1):S386.</p> <p>Annals of oncology [Internet]. 2015; 26:[i43</p>
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ctDNA= Circulating tumour DNA, NSCLC=non-small cell lung cancer.

Source: Table 8, pp33 of the resubmission.

6.9 The key features of the direct randomised trial AURA3 are summarised in the table below.

**Table 4: Key features of the included evidence**

Trial	N	Design/ Mean treatment duration*	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
<b>Osimertinib versus platinum-doublet chemotherapy</b>						
AURA3	419	R, OL Osimertinib arm: [redacted] months; Chemotherapy arm: [redacted] months	PFS: Low** OS/other: High	T790M mutation positive NSCLC patients who have failed prior EGFR TKI	PFS, response rate OS	Used

R=randomised; OL=open label; OS=overall survival; PFS=progression-free survival.

\*Exposure data only for September 2016 data cut-off. Exposure data for [redacted] data cut-off have not been provided in the resubmission. The CSR September 2016 data cut-off reported that the median follow-up for OS was [redacted] months for osimertinib and [redacted] months for chemotherapy. At the [redacted] cut-off, median follow-up for OS in all patients were [redacted] months and [redacted] months in the osimertinib and platinum based chemotherapy arms, respectively

\*\* low for PFS, but high for patient reported outcomes (such as adverse events, quality of life). High confounding of OS due to switching to osimertinib and lack of switching to nivolumab in AURA3.

Source: Compiled during the evaluation using data from Tables 14-5, pp41-2 of the resubmission.

### Comparative effectiveness

6.10 The results for progression free survival (PFS) at the September 2016 data cut-off, tumour response rates and patient reported outcomes were unchanged from the November 2017 submission. Overall, the results indicated that compared with platinum-based doublet chemotherapy:

- There was a difference in median PFS of 5.7 months and a statistically significant reduction in risk of progression or death of approximately 70% favouring osimertinib (hazard ratio [HR] 0.30 (95% CI: 0.23, 0.41));
- Superior tumour response rates favouring osimertinib for objective response rate (ORR: Odds ratio 5.39 (95% CI: 3.47, 8.48; p<0.001)) AND disease control rate (DCR: Odds ratio 4.76 (95% CI: 2.64, 8.84; p<0.001)); and
- The majority of the quality of life (QoL) categories favoured osimertinib.

6.11 The results for OS at 100% maturity (DCO September 2016, presented in the November 2017 submission and reproduced here for comparison purposes) and at 100% maturity (DCO [redacted]) are summarised in the tables below.

**Table 5: AURA3 Overall survival (interim ITT analysis, 100% maturity; data cut-off September 2016) – November 2017 submission**

Endpoint	Osimertinib N=279	Chemotherapy N=140	Treatment effect HR (95% CI)	p-value
Events (deaths), n (%)	█ (█)	█ (█)		
Median, months (95% CI) <sup>a</sup>	█ (█, █)	█ (█, █)	█	█
% survival by time point (95% CI) <sup>b</sup>			(█, █)	
6 months	█ (█, █)	█ (█, █)		
12 months	█ (█, █)	█ (█, █)		

Notes: At the time of the interim analysis, █% of patients in the chemotherapy arm had switched over to receive osimertinib.  
<sup>a</sup>Medians calculated using the Kaplan-Meier technique.  
 CI = confidence interval; ITT = intention-to-treat; NC = not calculable (not reached)  
 Source: 2017 osimertinib submission

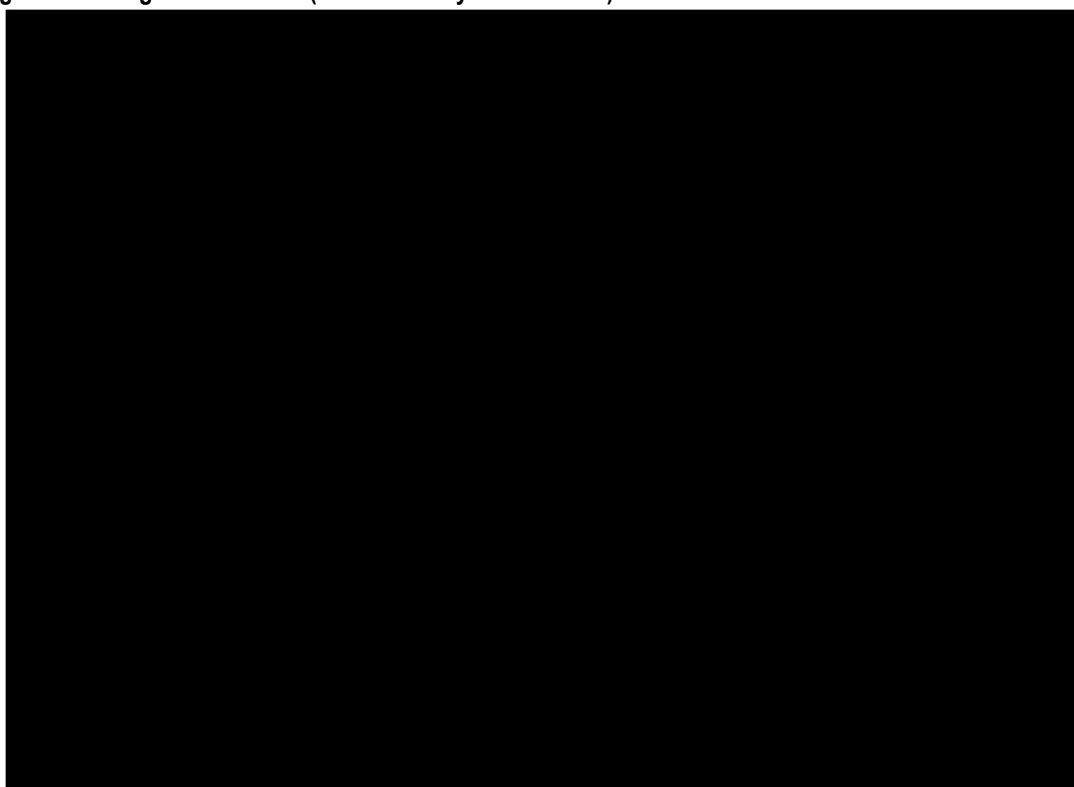
**Table 6: AURA3 Overall survival (interim ITT analysis, 100% maturity; data cut-off [redacted]) – resubmission**

Endpoint	Osimertinib N=279	Chemotherapy N=140	Treatment effect HR (95% CI)	p-value
Events, (deaths), n (%)	█ (█)	█ (█)		
Median, months (95% CI) <sup>a</sup>	█ (█, █)	█ (█, █)	(█, █)	█
	Difference: █ months			
% survival by time point (95% CI)				
• 6 months	█ (█, █)	█ (█, █)		
• 12 months	█ (█, █)	█ (█, █)		

Notes: At the time of the interim analysis, █% of patients in the chemotherapy arm had switched over to receive osimertinib.  
<sup>a</sup>Medians calculated using the Kaplan-Meier technique.  
 CI = confidence interval; NR = not reported, ITT = intention-to-treat  
 Source: Table 21, p49 of the resubmission.

- 6.12 Durations for median OS [REDACTED] the September 2016 DCO whilst for the [REDACTED] DCO, the median OS duration was [REDACTED] in the osimertinib arm than that observed for the platinum-based doublet chemotherapy arm. There was a [REDACTED]% reduction in risk of death associated with osimertinib over chemotherapy, which was [REDACTED]. A greater proportion of osimertinib-treated patients [REDACTED]. The resubmission conducted a statistical adjustment for post-progression treatment switching using the RPSFT model.

Figure 1: Counterfactual overall survival of patients randomised to osimertinib or randomised to chemotherapy assuming no switching to osimertinib (RPSFTM analysis of AURA3)



Source: Figure 18, p71 of the resubmission.

- 6.13 Based on the RPSFT analysis, if a patient randomised to chemotherapy started treatment with osimertinib, survival after treatment initiation was multiplied by [REDACTED] to estimate the counterfactual survival, had treatment with osimertinib not started. The adjusted HR between the two curves was estimated to be [REDACTED] with the corresponding p-value as that for the ITT analysis (95% CI: [REDACTED], [REDACTED]; p=[REDACTED]).
- 6.14 The attempt to adjust OS for treatment switching in the direct AURA3 trial was a more robust approach than the naïve indirect comparison presented in the

November 2017 submission. However, quantifying the OS benefit associated with osimertinib remained difficult, as the RPSFT model retained the p-value from the ITT analysis by design and therefore, in a setting where the point estimate of the HR was reduced, the 95% confidence intervals (CI) widened<sup>1-3</sup>.

- A key assumption of the RPSFT model is the “common treatment effect”<sup>4</sup>. If NSCLC patients who had progressed on platinum based chemotherapy partway through the trial, received a different treatment effect from osimertinib compared to patients originally randomised to osimertinib, the RPSFT analysis will be biased in favour of osimertinib. There is uncertainty regarding whether the common treatment effect is plausible in this specific case. An adequate clinical rationale/assessment of the validity of this assumption was not presented in the resubmission. The Pre-Submission-Committee Response (PSCR) maintained that who receive treatment with osimertinib in the third line setting are likely to receive the same relative magnitude of benefit as those who receive osimertinib in the second line setting. The PSCR also conducted a sensitivity analysis where the RPSFT was [REDACTED]

[REDACTED] The ESC considered that this analysis was useful and suggested a modest impact on the HR, but noted that the results of this sensitivity analysis could be verified due to the lack of relevant survival data.

- Two RPSFT methods were presented in the resubmission and resulted in HRs favouring osimertinib over platinum-based doublet chemotherapy [REDACTED]

[REDACTED] The ESC noted that the difference between the two methods was that [REDACTED]

- Additionally, no RPSFT analyses without recensoring were presented. The PSCR presented the RPSFT analysis with no recensoring. This resulted in a HR of [REDACTED], which was similar to that used in the submission ([REDACTED]), and [REDACTED] than the ITT HR of [REDACTED]. The ESC considered that this analysis was useful, as it provided further confidence about the robustness of the HR generated by the RPSFT analyses.

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<sup>4</sup>The treatment effect is assumed to be constant over time and the treatment effect received by control group patients who switched onto the experimental treatment is the same (relative to the time for which it was taken) as that received by patients initially randomised to the experimental group.

- The justification in the resubmission for not presenting an inverse probability of censoring weighted (IPCW) analysis and using only the RPSFT model to adjust OS in the chemotherapy arm of AURA3 for the clinical claim and the base case of the economic model is unsatisfactory. The resubmission argued that an IPCW analysis may not be appropriate as the extent of switching could lead to imprecise estimates of the HR. However, the IPCW approach, like the RPSFT, was not designed for efficiency gains, but rather to produce an unbiased estimate of the effect of treatment in the absence of switching.
  - The PSCR stated that in AURA3, the probability of switching was non-zero for only a short period with very few data points. Thus, it was unlikely that a credible model for the probability of switching could be developed and this precluded an informative IPCW analysis. The ESC considered that the PSCR had adequately clarified that among all [REDACTED] non-switchers, only [REDACTED] were eligible to switch (i.e. alive at the time of disease progression) and therefore considered that the PSCR's arguments against an IPCW model were reasonable.
  - The PSCR instead conducted a two-stage analysis fitting a Weibull accelerated failure time model to estimate post-progression survival in chemotherapy patients. This analysis demonstrated that when there were no covariates for the Weibull model, the estimated HR (Cox regression estimate for overall survival) was [REDACTED]. When the covariates were [REDACTED], the estimated HR was [REDACTED] when [REDACTED], and [REDACTED] when [REDACTED].
  - Taking all of the above evidence into consideration, the ESC considered that the additional two-stage analyses in the PSCR confirmed the robustness of the RPSFT analyses. However, the assumption of common treatment effect was the key issue. While the sensitivity analysis assuming [REDACTED]% attenuation of effect resulted [REDACTED] HR to those generated by the RPSFT analyses, it was unclear if this would hold true [REDACTED]. The ESC therefore advised that under the constraints of the available data, the RPSFT [REDACTED] [REDACTED] would be the more appropriate method of adjusting for crossover, since it [REDACTED].
- 6.15 Nivolumab is currently PBS listed for NSCLC patients who have progressed after platinum-based doublet chemotherapy. However, only [REDACTED]% of patients in the platinum-based doublet chemotherapy comparator arm of AURA3 subsequently received nivolumab upon progression (September 2016 data cut-off). Additionally, the resubmission claimed that the benefit of nivolumab, following failure on platinum-based doublet chemotherapy, was not superior to docetaxel monotherapy in EGFR mutation positive patients. The evidence provided in the resubmission was a retrospective analysis of a small subgroup of EGFR mutation positive patients from the CheckMate 057 trial, which compared nivolumab with docetaxel in the post-

platinum later-line setting. The PSCR argued that the reduced use of nivolumab in AURA3 did not present an applicability issue, citing a growing body of evidence, including Checkmate 057, two meta-analyses of checkpoint inhibitors<sup>5</sup> and “real world data sets”<sup>6</sup>, demonstrating that nivolumab is no better than single agent docetaxel in patients with EGFR mutation positive NSCLC. The ESC maintained that the resubmission had underestimated the benefit derived from nivolumab treatment, but acknowledged that the comparative benefit of nivolumab was hard to estimate, given the exploratory and indirect nature of these comparisons.

### Comparative harms

6.16 A general summary of adverse events (AEs) from the AURA3 trial is presented below.

**Table 7: AURA3 summary of adverse events**

AE category <sup>a</sup>	Osimertinib N=279	Chemotherapy N=136
Any AE, n (%)	273 (97.8)	135 (99.3)
Any AE possibly related to study treatment <sup>b</sup>	236 (84.6)	121 (89.0)
Any AE of CTCAE Grade 3 or higher	82 (29.4)	64 (47.1)
Any AE of CTCAE Grade 3 or higher, possibly related to study treatment <sup>b</sup>	20 (7.2)	45 (33.1)
Any AE with outcome = death	6 (2.2)	1 (0.7)
Any AE with outcome = death, possibly related to study treatment <sup>b</sup>	2 (0.7)	1 (0.7)
Any SAE	65 (23.3)	35 (25.7)
Any SAE, possibly related to study treatment <sup>b</sup>	10 (3.6)	17 (12.5)
Any AE leading to discontinuation of study treatment	22 (7.9)	15 (11.0)
Any AE leading to discontinuation of study treatment, possibly related to study treatment <sup>b</sup>	12 (4.3)	13 (9.6)

Note: Adverse event data unchanged from the previous submission (September 2016 data cut-off).

<sup>a</sup> Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category were counted once in each category.

<sup>b</sup> As assessed by the investigator, and programmatically derived from individual causality assessments. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of randomised treatment or the day before first administration of treatment switching.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event

Source: Table 22, p54 of the resubmission.

6.17 AEs with a higher incidence in the osimertinib arm than in the chemotherapy arm included (but were not limited to) diarrhoea (41% vs. 11%), paronychia (19% vs. 2%) and dermatitis (14% vs. 2%). AEs with a higher frequency in the chemotherapy arm included (but were not limited to) nausea (49% vs. 20%), anaemia (30% vs. 8%), neutropenia (13% vs. 4%), decreased platelet count (15% vs. 5%), and asthenia (15% vs. 7%). These AEs are consistent with the known class effects for EGFR TKI agents and platinum based chemotherapy.

<sup>5</sup> Lee CK, Man J, Lord S et al. J Thorac Oncol 2016;12(2):403-7 and Sheng Z, Zhu X, Sun Y et al. Oncotarget 2017; 8(34):57826-35

<sup>6</sup> Kobayashi K, Nakachi I, Naoki K et al. Clin Lung Cancer; 19(3):e349-58, Nishio M, Hida T, Atagi S et al. ESMO Open 2016 and Gainor J, Shaw A, Sequist L et al. Clin Cancer Res. 2016; 22(18):4585-93

## Benefits/harms

6.18 A summary of the comparative benefits and harms for osimertinib versus platinum-based doublet chemotherapy is presented in the table below.

**Table 8: AURA3: Summary of comparative benefits and harms for osimertinib and platinum-based doublet chemotherapy**

Benefits					
	Osimertinib <sup>1</sup> N = 279	Chemotherapy <sup>1</sup> N = 140	Absolute difference		HR (95% CI)
ITT analysis: Overall survival ((interim OS analysis [redacted] cut-off; [redacted] % maturity with [redacted] % switching from chemotherapy to osimertinib)					
Deaths, n (%) % surviving at 12 month - time point (95% CI)	[redacted] ([redacted]) [redacted] % ([redacted])	[redacted] ([redacted]) [redacted] % ([redacted])	[redacted] %		ITT analysis p-value = [redacted]
OS median months (95% CI)	[redacted] ([redacted])	[redacted] ([redacted])	[redacted]		RPSFT analysis (Method A) [redacted] ([redacted]) RPSFT analysis (Method B) [redacted] ([redacted])
RECIST-defined PFS (Investigator confirmed by independent review) <sup>3</sup>					
Progressed, n (%)	140 (50.2)	110 (78.6)	-		0.30 (0.23, 0.41) p-value <0.001
PFS median months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)	5.7 months		
Harms <sup>3</sup>					
	Osimertinib	Chemotherapy	Event rate/100 patients		RD% (95% CI)
			Osimertinib	Chemo	
Any AE of CTCAE Grade 3 or higher, possibly related to study treatment n/N	20/279	45/136	7.2	33.1	-25.9 (-34.4, -17.5)
Any SAE, possibly related to study treatment	10/279	17/136	3.6	12.5	-8.9 (-14.9, -2.9)

<sup>1</sup>Updated durations of exposure at [redacted] data cut-off were not reported in the resubmission. Median follow-up for OS in all patients were [redacted] months and [redacted] months in the osimertinib and platinum based chemotherapy arms, respectively [redacted]

<sup>3</sup>Unchanged from previous submission.

Italics were calculated for the previous November 2017 PBAC consideration

SAE = serious adverse event; CTCAE = Common Terminology Criteria for Adverse Events; PFS = progression free survival; HR = hazard ratio; RD = risk difference

Source: Compiled during the evaluation from Table 2-19, p80 of the main resubmission

6.19 On the basis of the AURA3 trial, treating T790M tumour positive advanced NSCLC patients (after failure of TKI therapy) with osimertinib rather than with platinum-based doublet chemotherapy for an average period of at least [redacted] months<sup>7</sup>:

<sup>7</sup> Updated durations of exposure for the [redacted] data cut-off were not reported in the resubmission and therefore a minimal average treatment duration (from the average treatment duration provided in the previous submission (November 2017 PBAC consideration) for data cut-off 2 September 2016, [redacted] % maturity) has been used in the balance of benefits and harms.

- There was a significant improvement in median PFS of approximately 6 months associated with osimertinib (PFS data from AURA3 have not changed from that presented in the previous submission);
  - The OS benefit associated with osimertinib from AURA3 was uncertain. The updated OS data were immature and potentially confounded from platinum-based doublet chemotherapy treated patients switching upon progression. In addition, the chemotherapy arm of AURA3 has limited applicability to Australian clinical practice as it excluded subsequent treatment and benefits with nivolumab:
    - Based on the most conservative results from the ITT analysis (that were not modelled) at █% OS maturity (median follow-up ranging from █ to █ months), treatment with osimertinib compared with platinum-based doublet chemotherapy, resulted in:
      - approximately █ additional patients alive at █ months; and a reduction in the risk of death of approximately █% which was █.
    - Based on an analysis which adjusted the OS for the platinum-based doublet chemotherapy group to remove the effect of subsequent treatment with osimertinib, there was a █% reduction in the risk of death associated with osimertinib; however, this benefit is unlikely to be realised in Australian clinical practice due to limitations with the modelling approach used and the lack of consideration of PBS subsidised nivolumab impacting on the comparator's treatment effect.
- 6.20 For every 100 patients treated with osimertinib in comparison to chemotherapy, 26 fewer patients would experience a Grade 3 or higher, drug - related adverse event and 9 fewer patients would have a serious drug-related adverse event when treated with osimertinib instead of with chemotherapy. This has not changed from the previous submission.

### **Clinical claim**

- 6.21 The submission described osimertinib as superior in terms of effectiveness and superior in terms of safety compared to platinum based chemotherapy.
- 6.22 The claim is reasonable in terms of response rates, PFS and AEs observed from the direct AURA3 trial. However, the claim regarding OS is not adequately supported as there is uncertainty regarding the magnitude of the OS benefit:
- The ITT analysis indicated a HR of █ which was not statistically significant, albeit █% of trial participants switched from platinum-based doublet chemotherapy to osimertinib upon progression;

- It was based on a modelled RPSFT HR of [REDACTED] which should be interpreted with caution given the uncertainty of the underlying assumptions and the lack of other adjustment approaches to enable examination of the robustness of the RPSFT approach;
  - Few patients in the platinum-based doublet chemotherapy arm of AURA3 received subsequent treatment with nivolumab ([REDACTED]%) following progression. As nivolumab is listed on the PBS for this population, this may underestimate OS associated with nivolumab in Australian clinical practice.
- 6.23 The ESC noted that the PSCR explored several alternative methods to adjust for crossover in AURA3, and advised that the HR generated by the RPSFT [REDACTED] analysis was the more appropriate in this context.
- 6.24 The ESC noted that for the ITT analysis a [REDACTED] on OS was estimated with more mature data provided in the resubmission compared with that provided in the original submission (HR=[REDACTED] vs [REDACTED]), and the difference in OS [REDACTED]
- 6.25 Considering all the clinical evidence and statistical analyses for crossover adjustment presented in the resubmission, the PBAC advised that although osimertinib treatment was effective compared with platinum chemotherapy in relation to PFS, the uncertainty in crossover adjustment of the OS data remained that key confounding factor. As such, the magnitude of the overall survival benefit of osimertinib treatment compared with chemotherapy remained uncertain.
- 6.26 The PBAC noted that the comparative harms of osimertinib treatment were unchanged from the previous submission, and advised that it was superior in safety compared with platinum chemotherapy.

### ***Economic analysis***

- 6.27 The resubmission presented a modelled economic evaluation, based on the direct AURA3 trial. The type of economic evaluation presented was a cost-effectiveness analysis and a cost-utility analysis, measuring outcomes in terms of life-years (LYs) gained and quality-adjusted life years (QALYs) gained, respectively. The key components of the economic evaluation are summarised below.

**Table 9: Summary of model structure and rationale**

Component	Summary
Type of analysis	Cost-effectiveness analysis and cost-utility analysis
Outcomes	LYs gained and QALYs gained
Time horizon	10 years in the model base case vs median follow-up of ██████-day months in osimertinib patients and ██████ months in the re-censored RPSFT analysis for chemotherapy patients in AURA3. The resubmission selected the time horizon based on the time at which the large majority of patients had died. The time horizon of the economic model remained the same as in the previous submission. The PBAC previously considered that the choice of a 10-year time horizon was unrealistically long for patients with NSCLC receiving second-line treatment and therefore implausible and overly optimistic (osimertinib Public Summary Document (PSD), November 2017 PBAC meeting).
Methods used to generate results	Markov cohort expected value analysis
Health states	Four health states: <ul style="list-style-type: none"> <li>- Progression-free on treatment with osimertinib;</li> <li>- Progression-free on treatment with platinum-based doublet (either in the 2<sup>nd</sup>-line setting in patients not treated with osimertinib, or 3<sup>rd</sup>-line setting in a proportion of osimertinib-treated patients)</li> <li>- Progressive disease (managed by salvage therapy or BSC);</li> <li>- Death</li> </ul> <p>The use of a four-health state model for patients who begin on second-line osimertinib was not adequately justified. It was not convincing that two separate progressive disease health states were warranted for patients who start on osimertinib, and only one for patients who start on chemotherapy.</p>
Utilities	Progression-free utilities: AURA3 Progressive disease: IMPRESS The resubmission did not justify the assumption that the utility was the same between patients receiving 2 <sup>nd</sup> -line chemotherapy and those treated with chemotherapy as 3 <sup>rd</sup> -line therapy following failure of 2 <sup>nd</sup> -line osimertinib. This assumption marginally favoured osimertinib.
Cycle length	30 days For every cycle 1/12 of a QALY or LY is gained rather than 30/365ths, which equates to 30.4 days and marginally favoured osimertinib.
Transition probabilities	Transition probabilities from the two progression-free health states to other health states were estimated using the PFS data from the relevant treatment arm of AURA3. Transition probabilities from the progressive disease to the death health states were calculated on the basis of the AURA3 PFS and OS data. Due to ██████ (█████%) treatment switching from doublet chemotherapy to osimertinib upon disease progression in AURA3, in the base case, the RPSFT method has been used to estimate survival of patients in the comparator chemotherapy arm. The selection of the RPSFT method for the base case method (and specifically the more optimistic of the two RPSFT methods tested) has not been adequately justified, although the ITT-based estimate is used in a sensitivity analysis. Constant transition probabilities were assumed in the model beyond the median follow-up of the AURA3 trial. The assumption of constant transition probabilities implied an ongoing treatment effect associated with osimertinib, which was not justified. This favoured osimertinib.
Software package	TreeAge Pro

BSC = best supportive care; ITT = intention-to-treat; LYs = life-years; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; PSD = public summary document; QALYs = quality-adjusted life years; RPSFT = rank-preserving structural failure time

Source: Table 37, p84 of the resubmission.

6.28 The key differences in model inputs/assumptions between the previous submission and the current resubmission are summarised below.

**Table 10: Main differences in model inputs/assumptions between the previous and the current submissions**

Assumption	November 2017 codependent submission	Current major resubmission to PBAC	Rationale provided in the resubmission
Population included in the model	All patients who failed EGFR TKI therapy, regardless of EGFR T790M mutation status.	EGFR T790M mutation true positive patients.	When considering the November co-dependent submission, MSAC foreshadowed its support for EGFR T790M testing.
OS efficacy data	Patients treated with osimertinib based on T790M positive patients from the pooled single-arm AURA1C and AURA2 studies. Patients treated with chemotherapy taken from the control arm of Trial IMPRESS.	Data taken from AURA3 (██████████ data cut) for both osimertinib and chemotherapy arms. RPSFT method was used to adjust for substantial treatment switching in the chemotherapy arm.	As requested by the PBAC to reduce the uncertainty associated with the OS data from the indirect comparison.

EGFR = epidermal growth factor receptor; OS = overall survival; RPSFT = rank-preserving structural failure time; TKI = tyrosine kinase inhibitor

Source: Table 36, p83 of the resubmission

6.29 The resubmission’s base case analysis, estimating the cost-effectiveness of treating EGFR T790M mutation positive patients with osimertinib compared to treating them with chemotherapy, would be appropriate only if all NSCLC patients who fail prior EGFR TKI are tested for EGFR T790M mutation in current clinical practice. This is not the case, as the MSAC deferred its advice “until such time as the PBAC subsequently decides to recommend the PBS listing of osimertinib for the requested population” (Application 1407 PSD, November 2017 MSAC meeting). Therefore, the base case model relating to this resubmission should compare a scenario where all NSCLC patients who fail EGFR TKI therapy undergo EGFR T790M testing and receive osimertinib for test positive or doublet chemotherapy for test negative (proposed scenario) against a scenario where EGFR T790M testing is not available and all patients are treated with doublet chemotherapy following EGFR TKI treatment failure (current scenario). Whilst this comparison was presented in the resubmission as a sensitivity analysis, it was defined as the base case economic analysis in the Commentary. The incremental cost-effectiveness ratio (ICER) from the Commentary’s base case model was higher than that from the submission’s base case model (\$75,000/QALY – \$105,000/QALY vs \$45,000/QALY – \$75,000/QALY). The ESC advised that the Commentary’s base case was appropriate.

6.30 In the November 2017 submission, the OS benefit of osimertinib compared with platinum-based doublet chemotherapy was based on a naïve indirect comparison of the pooled single-arm AURA1C and AURA2 studies (osimertinib) with the IMPRESS study (platinum doublet chemotherapy). This was one of the major areas of economic uncertainty raised by the PBAC (Osimertinib PSD, November 2017 PBAC meeting). The current resubmission used the direct AURA3 ITT results with adjustment for treatment switching via a RPSFT ██████████ analysis. As discussed above, the ESC considered that adjustment for crossover was appropriate, but advised that the RPSFT ██████████ method was the more appropriate method of

crossover adjustment, and therefore the HR generated using this method should be used in the economic model instead.

- 6.31 The health states, allowable transitions and associated utilities in the resubmission were unchanged from previous submission. The resubmission did not justify why the second-line data observed from the chemotherapy arm in AURA3 for progression free survival apply to the third-line setting, where patients in the osimertinib arm transition from third-line chemotherapy to fourth-line best supportive care (BSC). This approach affected the QALYs gained after osimertinib treatment, as the same utility was applied with second-line chemotherapy as for third-line chemotherapy. This assumption favoured osimertinib.
- 6.32 The previous submission selected a 10-year time horizon for the economic model. The PBAC considered that the submission's choice of a base case 10-year time horizon was unrealistically long and therefore implausible and overly optimistic (Osimertinib PSD, November 2017 PBAC meeting). The resubmission argued that a 10-year time horizon was appropriate based on the extrapolated survival curves in the model.
- The extrapolation of survival curves in the model assumed a constant transition probability beyond the trial period, and a lower probability of death for patients receiving second-line osimertinib than those receiving second-line chemotherapy. This implied a continuous superior treatment effect of osimertinib to chemotherapy during the progressive disease health state where these treatments have already discontinued. This assumption was not supported by any clinical evidence and was unrealistic. The PSCR argued in favour of an ongoing treatment effect, noting that (i) during trial follow-up, a [REDACTED] month increase in median PFS translated into a [REDACTED] month increase in median OS (after adjusting for treatment switching), and (ii) rate of death was lower in the osimertinib arm within the trial period. The ESC considered that this was not sufficient to justify the plausibility of an ongoing treatment effect in the extrapolated period, which constituted approximately [REDACTED]% of the modelled time horizon.
  - The PSCR presented a sensitivity analysis where the overall survival extrapolation in both groups was forced to zero at 7.5 years based on a linear extrapolation after 5 years. This increased the ICER to \$75,000/QALY to \$105,000/QALY. If the model was simply truncated to 7.5 years, the ICER was \$75,000/QALY to \$105,000/QALY with [REDACTED]% of osimertinib patients remaining alive. The ESC noted that ICER would be \$75,000/QALY to \$105,000/QALY when a 5-year time horizon is used.
  - The ESC noted the resubmission's arguments in favour of a 10-year time horizon, but taking into account the duration of follow-up in AURA3 ([REDACTED] months for osimertinib OS) and previous PBAC consideration (5-year time horizon in first-line setting), maintained that a 5-year time horizon is more

appropriate in the base case analysis. However, the ESC acknowledged that the model was only moderately sensitive to the duration of the time horizon between 5 and 10 years.

- 6.33 The cost of osimertinib applied to the model may be an underestimate, as it was based on the observed truncated mean duration of treatment on osimertinib in the AURA3 trial (■ months) where a ■ proportion of patients (■%) remained on osimertinib. The duration of PFS for the osimertinib arm of the economic model was ■ months. The PSCR reaffirmed the sponsor's position that the mean actual treatment duration reported (■ months) provided the best estimate of likely utilisation in practice. The ESC disagreed, noting that a truncated mean for the treatment duration from the trial will not reflect utilisation in practice.
- 6.34 As noted earlier, nivolumab was used in a small proportion of patients after disease progression in AURA3 (around ■%) in both treatment arms. Therefore, any benefit associated with its use was not captured. As nivolumab following platinum-based doublet chemotherapy is currently listed on the PBS, the economic model assumed that ■% of patients who receive second-line chemotherapy would be treated with nivolumab (unchanged from the previous submission). The PBAC had noted that the ■% may be an overestimate due to the PBS listing requirement of a performance status of 0-1. However there were no data to refute this estimate (Osimertinib PSD, November 2017 PBAC meeting). More importantly, the economic model took into account the cost offset related to third-line nivolumab following doublet chemotherapy but assumed no additional survival benefits from nivolumab therapy. The ESC considered that this was unreasonable and noted that it biased the result in favour of osimertinib.
- 6.35 As the incremental costs appear underestimated, and the incremental outcomes may have been overestimated, the ICER is likely to be an underestimate.
- 6.36 The key drivers of the model are summarised below.

**Table 11: Key drivers of the model**

Description	Method/Value	Impact
OS in patients treated with platinum doublet chemotherapy if they do not switch to osimertinib upon disease progression	In AURA3, around █% of patients receiving doublet chemotherapy switched to osimertinib after disease progression. The RPSFT method was used to estimate the survival of patients in the chemotherapy arm.	High, favours osimertinib
Extrapolation of transition probabilities from progressive disease to death	The resubmission assumed a constant transition probability from progressive disease to death beyond the extrapolation time point (Cycle █ for osimertinib and Cycle █ for chemotherapy). The lower constant transition probability for osimertinib than that for doublet chemotherapy (█ vs █) implied an ongoing treatment effect associated with osimertinib, which was not justified.	High, favours osimertinib
Time horizon	10 years	Moderate, favours osimertinib
Cost of osimertinib	The resubmission applied an one-off treatment course cost based on the truncated mean duration of treatment observed in the AURA3 trial (█ months), compared to a modelled mean duration in the 'progression-free on osimertinib' health state of approx. █ months	Moderate, favours osimertinib
The use of third-line nivolumab after disease progression on chemotherapy	The resubmission assumed that █% of patients who progress on second-line chemotherapy would receive nivolumab. The economic model costed third-line nivolumab therapy, but assumed no additional health benefits from this use.	Moderate, favours osimertinib

OS = overall survival; RPSFT = rank-preserving structural failure time  
Source: Compiled during the evaluation

6.37 The results of the co-dependent economic model are summarised below.

**Table 12: Results of the stepped economic evaluation (co-dependent model)**

	Costs			Health outcomes			ICER
	T790M/Osi available	No testing + Chemo for all	Increment	T790M/Osi available	No testing + Chemo for all	Increment	
Step 1 Trial setting (T790M+ only) Time horizon: █ months <sup>a</sup>	█	█	█	█% ORR	█% ORR	█% ORR	\$ █ per additional responder
Step 2 Proposed MBS and PBS populations Time horizon: 10 years	█	█	█	█ LYs	█ LYs	█ LYs	\$ █ per LY gained
Step 3 Study evidence transformed from LY to QALY	█	█	█	█ QALYs	█ QALYs	█ QALYs	\$ █ per QALY gained

ORR = objective response rate; LY = life year; QALY = quality-adjusted life year.

<sup>a</sup> Median time until loss of response for osimertinib

Source: Table 64, p144 of the resubmission. Results in italics were calculated during the evaluation based on "Model – osimertinib – NSCLC" TreeAge, after correcting the reference errors in the p→d transition probabilities as summarised in Table 3.4.4

The redacted table shows ICERs in the range of \$45,000 - \$200,000.

6.38 The key sensitivity analyses conducted during the evaluation are summarised below.

**Table 13: Results of key sensitivity analyses (co-dependent model)**

	Assumptions	Incremental costs	Incremental QALYs	ICER	% change
<b>Base case</b>					
<b>Univariate analyses</b>					
1	Time horizon of 5 years (base case: 10 years)				%
2	Using the ITT OS data for chemotherapy (base case: RPSFT method to adjust treatment switching)				%
3	Assuming the transition probability from progressive disease to death for osimertinib the same as for chemotherapy (T790M mutation positive) ( ) from Cycle 30 onwards (base case: )				%
4	Cost of osimertinib applied in each cycle while in progression-free on osimertinib health state, taking into account the daily dose intensity and the ratio of time-on-treatment to PFS (base case: fixed cost of \$ per course)				%
5	Third-line nivolumab use in % of patients after disease progression on chemotherapy (base case: %)				%
6	No third-line nivolumab use after disease progression on chemotherapy (base case: %)				%
<b>Multivariate analyses</b>					
#1 AND #3					%
#1 AND #4					%
#1 AND #3 AND #4					%

ICER = incremental cost-effectiveness ratio; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; QALY= quality-adjusted life year; RPSFT = rank-preserving structural failure time

Source: Sensitivity analyses performed during the evaluation based on “Model – osimertinib – NSCLC” TreeAge, after correcting the reference errors in the p→d transition probabilities as summarised in Table 3.4.4.

The redacted table shows ICERs in the range of \$75,000/QALY – \$200,000/QALY.

6.39 The main clinical and economic uncertainty was the relative treatment effect of osimertinib versus doublet chemotherapy in terms of OS. Results from the sensitivity analysis indicated that the economic model was highly sensitive to the magnitude of OS difference.

6.40 The model was also highly sensitive to the transition probabilities from progressive disease to death. Assuming identical transition probabilities for second-line doublet chemotherapy and second-line osimertinib for all cycles, the ICER would increase from \$75,000/QALY – \$105,000/QALY to \$105,000/QALY – \$200,000/QALY.

6.41 Changes in the time horizon of the economic model, the cost for osimertinib per treatment course, and the use of third-line nivolumab following doublet chemotherapy would moderately affect the result of the economic evaluation.

6.42 The ESC noted that the proportion of patients with an Asian background in AURA3 was considerably higher than in Australian practice (65% vs 23%) and that a subgroup analysis suggested that numerically, the effect of osimertinib in patients of Asian origin, was higher (HR of [ ] vs [ ]). The ESC

considered that adjusting for this in the economic model was likely to increase the ICER further.

- 6.43 The ESC noted that a multivariate sensitivity analysis assuming (i) a 5-year time horizon; (ii) no ongoing treatment effect and (iii) treatment until progression (i.e. taking into account the daily dose intensity and the ratio of time-on-treatment to PFS) resulted in an ICER of \$105,000/QALY – \$200,000/QALY. This analysis assumed an OS HR of [REDACTED] i.e. that generated using the RPSFT-[REDACTED]. The ESC advised that the ICER generated using the three assumptions above, along with the OS HR generated by the RPSFT ([REDACTED]) analysis, i.e. [REDACTED], would provide a more accurate estimate of the cost-effectiveness of osimertinib. The ESC noted that the model provided did not allow the sensitivity analysis for an alternative HR to be performed, as the model utilised survival data for each arm, and therefore the HR was not an input parameter.
- 6.44 The pre-PBAC response claimed that the multivariate analysis suggested by the ESC represented a scenario that was highly unlikely to occur in practice, contending that (i) a 5 year time horizon was not appropriate since a ‘sizable’ proportion of patients remained alive after 5 years; (ii) assuming no ongoing treatment effect was ‘unrealistically conservative’; (iii) the costed treatment duration ([REDACTED] months) provides the best estimate of the cost of osimertinib in practice; and (iv) the ESC’s preferred method of crossover adjustment, i.e. the RPSFT [REDACTED], was an outlier, compared with other methods outlined in the PSCR.
- 6.45 The pre-PBAC response also offered [REDACTED], increasing the proposed rebate from [REDACTED]% to [REDACTED]%. Applying this to the Commentary base case of \$75,000/QALY – \$105,000/QALY, reduced the ICER to \$45,000/QALY – \$75,000/QALY. The pre-PBAC response then proposed that this ICER could be further reduced to \$45,000/QALY – \$75,000/QALY, [REDACTED]. Details of this proposal are discussed in the “Financial Management – Risk Sharing Arrangements” section below.

**Drug cost/patient/course: \$76,646**

- 6.46 The treatment course cost per T790M mutation positive patient was \$[REDACTED]. This was based on [REDACTED] months of osimertinib at the proposed effective DPMQ of \$[REDACTED] per month. The ESC considered that the treatment duration of [REDACTED] months was likely an underestimate as it was based on the observed truncated mean duration of treatment on osimertinib in the AURA3 trial without extrapolation. The ESC therefore advised that the drug cost/patient/course was likely to be an underestimate.
- 6.47 The cost of chemotherapy, including pemetrexed maintenance and administration, per T790M mutation positive patient was \$5,732.

**Estimated PBS usage & financial implications**

6.48 This resubmission was not considered by DUSC.

6.49 The resubmission used an epidemiological approach to estimate the extent of use and cost implications associated with proposed listing of osimertinib. These were based on Australian Institute of Health and Welfare (AIHW) estimates, commissioned market research data and relevant literature. The estimated use and financial implications for the health budget are summarised in the table below.

**Table 14: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of patients treated	■	■	■	■	■	■
Number of scripts dispensed <sup>a</sup>	■	■	■	■	■	■
<b>Estimated financial implications of osimertinib<sup>b</sup></b>						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS/RPBS less copayments	■	■	■	■	■	■
<b>Estimated financial implications for reduction in use of chemotherapy, pemetrexed maintenance and nivolumab use</b>						
Cost to PBS/RPBS	■	■	■	■	■	■
Copayments	■	■	■	■	■	■
Cost to PBS/RPBS less copayments	■	■	■	■	■	■
<b>Net financial implications</b>						
Net cost to PBS/RPBS	■	■	■	■	■	■
Net cost to MBS Revised <sup>c</sup>	■	■	■	■	■	■
Net cost to Government Revised	■	■	■	■	■	■

<sup>a</sup> Assuming ■ scripts per patient as estimated by the resubmission.

<sup>b</sup> The cost of osimertinib to the PBS/RPBS was estimated using its proposed effective price.

<sup>c</sup> The net cost to the MBS has been revised to take into account the appropriate MBS benefit and patient contributions. The MBS cost for T790M testing was revised on the basis of the average fee charged to patients for current MBS-funded EGFR tests, the proportion of these services which are conducted in the outpatient setting and the proportion of these services which are bulkbilled, as reported in the Report to the Medical Services Advisory Committee on real world outcomes of Application 1161 PSD, November 2016. The MBS cost for biopsy was revised by assuming that in 65% of services, the 85% MBS benefit applies, and in 35% of services, the 75% MBS benefit applies (as per Section 3.6.1 of the resubmission). The MBS cost associated with chemotherapy administration was revised: 1) to assume 4 administration services of gemcitabine apply, as the service associated with carboplatin use will cover gemcitabine administration on Day 1 of each chemotherapy cycle; 2) to assume 6 administrations per patient for nivolumab, rather than 1 administration per patient as costed in the analysis; and 3) to assume that in 8.5% of services, the 75% MBS benefit applies, and in the remainder of services, the 85% MBS benefit applies (as per Section 3.6.4 of the resubmission).

Source: Table 72, p153, Table 77, p155, Table 86, p159 Table 87, p160 and Table 93, p163 of the resubmission.

The redacted table shows that at year 6, the estimated number of patients was less than 10,000 and the net cost to the PBS would be \$20 – \$30 million.

6.50 The inputs/assumptions used to estimate the extent of use of osimertinib were unchanged from the November 2017 submission, except for a higher number of

grandfathering patients (█ vs █), i.e. the estimated number of patients taking osimertinib via a temporary compassionate access program.

- 6.51 At the November 2017 meeting, the PBAC noted the concerns surrounding the duration of osimertinib use in clinical practice and the risk of leakage to first-line use (Osimertinib PSD, November 2017 PBAC meeting). Although the PSCR argued that the risk of leakage to first-line therapy was likely to be extremely small owing to the requirement of a written authority, the ESC advised that there was a high likelihood of leakage into first-line therapy, given the recently published results of the FLAURA trial<sup>8</sup>, for first-line osimertinib treatment of EGFR mutation positive NSCLC. The resubmission proposed a RSA to address the uncertainty with respect to expenditure (refer to the “Financial Management – Risk Sharing Arrangements” section below).

### **Financial Management – Risk Sharing Arrangements**

- 6.52 The sponsor expressed its willingness to enter into a confidential RSA with the Commonwealth based on the total cost of osimertinib to the PBS/RPBS. █

- 6.53 The pre-PBAC response maintained that leakage to first-line therapy was unlikely to occur in practice, due to (i) written authority approval requirements of the proposed restriction’ (ii) requirement of treatment with a prior TKI in the proposed restriction; and (iii) the fact that T790M resistance mutations develop after exposure to a TKI.

- 6.54 The pre-PBAC response proposed that any remaining concerns regarding the cost-effectiveness of osimertinib could be mitigated through █. The pre-PBAC response noted that █ the resulting ICER decreased from to \$45,000/QALY – \$75,000/QALY █

- 6.55 █

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<sup>8</sup> Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018;378:113-25.

**Table 15. Effect of proposed expenditure caps on the financial estimates – pre-PBAC response**

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of osimertinib patients	█	█	█	█	█
Submission estimates	█	█	█	█	█
Proposed expenditure cap	█	█	█	█	█
	█	█	█	█	█
	█	█	█	█	█

Source: Assuming █ scripts per patient as estimated by the resubmission.

For more detail on PBAC’s view, see section 7 PBAC outcome.

## 7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation to list osimertinib for the treatment of EGFR T790M mutation positive non-small cell lung cancer, requesting further clarification from the sponsor regarding the proposed risk sharing arrangement and utilisation estimates. In deciding to defer, the PBAC acknowledged that osimertinib treatment provided a clinical benefit to some patients, but considered that the magnitude of the incremental overall survival benefit was difficult to determine from the available evidence.
- 7.2 The PBAC advised that the criterion ‘The patients must have a WHO performance status of 2 or less’ be added to the proposed restriction to maintain alignment with the restrictions of the currently PBS-listed first line TKIs, i.e. erlotinib and gefitinib.
- 7.3 The PBAC noted that at its November 2017 consideration of EGFR T790M mutation testing for osimertinib treatment, the MSAC had deferred its advice until such time as the PBAC subsequently decides to recommend the PBS listing of osimertinib for the requested population. The PBAC also noted that in deferring its consideration, the MSAC had foreshadowed its support for a new MBS item for EGFR T790M mutation testing in tumour tissue obtained after progression on or after therapy with a TKI to determine eligibility for PBS-subsidised second-line osimertinib for the targeted treatment of patients with locally advanced (stage IIIB) or metastatic (stage IV) EGFR mutation positive NSCLC. This support was subject to a PBAC recommendation to list osimertinib once PBAC’s concerns regarding the medicine’s cost effectiveness were resolved.
- 7.4 The PBAC recalled that at its November 2017 consideration of osimertinib, it had advised that the clinical place in therapy and comparator (i.e. platinum-based doublet chemotherapy) proposed by the submission were appropriate (paragraphs 7.4 and 7.5, November 2017 osimertinib PSD). The PBAC noted that osimertinib was listed as a preferred first-line treatment in several international treatment guidelines due to its progression free survival benefit and tolerability profile versus first line TKIs i.e. erlotinib and gefitinib. The PBAC maintained that there was a high risk of leakage to first-line therapy, however noted that a written authority necessitating proven T790M mutation positive status would ameliorate this risk of leakage. The

PBAC noted that currently available evidence<sup>9</sup> demonstrated improved efficacy of first-line osimertinib treatment, and advised that it would welcome a submission for such a listing.

- 7.5 The PBAC recalled that the November 2017 submission for osimertinib was partly based on a direct randomised trial (AURA3) comparing osimertinib to platinum-based chemotherapy in the requested population, with PFS as the primary outcome. At its November 2017 consideration, the PBAC had considered that OS data from AURA3 was immature, with the interim analysis conducted at █% maturity. The PBAC had noted that a major confounding factor was that the OS results were contaminated as █% of patients randomised to the chemotherapy arm had switched to osimertinib upon progression at the time of the interim analysis. Importantly, instead of adjusting for treatment switching in the AURA3 trial, the November 2017 submission had presented a naïve indirect comparison between subgroups from single-arm studies (AURA Pooled [AURA1C and AURA2] for osimertinib and chemotherapy arm from the IMPRESS trial) to claim an overall survival advantage in favour of osimertinib. The PBAC recalled its advice that AURA3 data with statistical adjustment for crossover should have been used instead, since the less scientifically rigorous naïve indirect comparison presented in the submission introduced more, rather than less, uncertainty (paragraphs 7.7 and 7.8, November 2017 osimertinib PSD).
- 7.6 The PBAC noted that the resubmission presented updated OS data from AURA3 (DCO █; █% maturity) with adjustment of OS for treatment switching (█% switching from chemotherapy to osimertinib) using the RPSFT model (Method A). The PBAC noted that two RPSFT methods were presented in the resubmission and resulted in HRs favouring osimertinib over platinum-based doublet chemotherapy █. Additionally, the PSCR presented several sensitivity analyses to demonstrate the robustness of the RPSFT analyses. The PBAC noted that although the resubmission presented █ as the preferred choice of crossover adjustment, the ESC advised that under the constraints of the available data, the RPSFT █ would be the more appropriate method of adjusting for crossover, since it adjusted for the actual time spent on osimertinib after switching.
- 7.7 Considering all the clinical evidence and statistical analyses for crossover adjustment presented in the resubmission, the PBAC advised that although osimertinib treatment was effective compared with platinum chemotherapy in relation to PFS, the magnitude of the OS benefit of osimertinib treatment compared with chemotherapy remained uncertain. The PBAC noted that the comparative harms of

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<sup>9</sup> Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018;378:113-25.

osimertinib treatment were unchanged from the previous submission, and advised that it was superior in safety compared with platinum chemotherapy.

- 7.8 The PBAC recalled that the November 2017 submission had presented a modelled cost-utility analysis, using AURA3 to inform PFS, and the naïve indirect comparison to inform OS, with a time horizon of 10 years. The PBAC recalled that this model was critiqued by the ESC and the PBAC due to several structural issues, and for confounding due to the use of OS data from single-arm studies (AURA Pooled and IMPRESS) instead of the randomised trial (AURA3) to inform the economic model (paragraph 7.13, November 2017 osimertinib PSD).
- 7.9 The PBAC noted the resubmission's economic model was based on data from the AURA3 trial, adjusted for crossover using RPSFT [REDACTED]. The PBAC noted that the base case ICER presented in the resubmission (\$45,000/QALY – \$75,000/QALY) did not account for osimertinib's co-dependency on the MBS listing of the EGFR T790M mutation listing. As a result, the Commentary used a respecified base case ICER of \$75,000/QALY – \$105,000/QALY. The PBAC advised that this was appropriate.
- 7.10 The PBAC noted that the ESC identified several issues with the resubmission's economic model. The PBAC noted the ESC's advice that a multivariate sensitivity analysis assuming (i) a 5-year time horizon; (ii) no ongoing treatment effect and (iii) treatment until progression (i.e. taking into account the daily dose intensity and the ratio of time-on-treatment to PFS), and (iv) the OS HR generated by the RPSFT ([REDACTED]) analysis, i.e. [REDACTED], would provide a more accurate estimate of the cost-effectiveness of osimertinib. The PBAC further noted incorporating (i), (ii) and (iii), increased the ICER from \$75,000/QALY – \$105,000/QALY to \$105,000/QALY – \$200,000/QALY, and that the impact of changing the HR on the ICER could not be tested using the model provided.
- 7.11 The PBAC noted that the pre-PBAC response presented several arguments to demonstrate that the multivariate analysis suggested by the ESC represented a scenario that was highly unlikely to occur in practice. The pre-PBAC response also argued that when the various assumptions of the ESC's preferred multivariate scenario were applied, the economic model generated a HR for OS of [REDACTED], i.e. worse than the ITT ([REDACTED]). The PBAC advised that this argument was not justified, as it was inappropriate to compare the modelled HR with the ITT HRs used within the trial period, given that the validity of the proportional hazard assumption beyond the trial period was unknown.
- 7.12 The PBAC also noted that the pre-PBAC response presented a further price reduction which reduced the Commentary base case of \$75,000/QALY – \$105,000/QALY to \$45,000/QALY – \$75,000/QALY.
- 7.13 The PBAC noted the sponsor's proposal in the pre-PBAC response stating that any remaining concerns regarding the cost-effectiveness of osimertinib could be mitigated through [REDACTED] via a risk sharing agreement.

The pre-PBAC response noted that if a [REDACTED] the resulting ICER decreased to \$45,000/QALY – \$75,000/QALY in the [REDACTED]. The pre-PBAC response subsequently [REDACTED]

- 7.14 The PBAC advised that further information regarding the risk share agreement proposed in the pre-PBAC response would be required in the form of a minor resubmission. The PBAC advised that the resubmission should address the estimated number of treated patients (noting that the patient numbers were revised in the pre-PBAC response) together with the estimated expenditure and financial caps in each of the first five years of listing, and these estimates should appropriately account for grandfathered patients. The PBAC advised that the risk share arrangement should incorporate a rebate [REDACTED] % for expenditure above the agreed financial caps. The minor resubmission should also present the ICERs for the both the Commentary base case and the ESC multivariate sensitivity analysis, and the impact of changing the OS HR on the ICER should be explored.

**Outcome:**

Deferred

## 8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

## 9 Sponsor's Comment

The sponsor had no comment.