5.12 OSIMERTINIB, Tablet 40 mg, tablet 80 mg Tagrisso®, AstraZeneca Pty Ltd

1 Purpose of submission

1.1 The submission requested a Pharmaceutical Benefits Schedule (PBS) listing of osimertinib for the targeted treatment of patients with locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer (NSCLC), who have evidence of a *T790M* mutation of the epidermal growth factor receptor (*EGFR*) gene following progression on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

1.2 The integrated codependent submission also requested that the Medical Services Advisory Committee consider a Medical Benefits Schedule (MBS) listing of *EGFR T790M* mutation testing.

Table1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Test: Locally advanced or metastatic NSCLC patients, who have disease progression on or after treatment with an EGFR TKI Medicine: Locally advanced or metastatic NSCLC patients who are *T790M* mutation positive and who have disease progression on or after treatment with an EGFR TKI
Intervention	Test: *EGFR* mutation test to determine *T790M* status Medicine: If *T790M* mutation positive, receive osimertinib If *T790M* mutation negative or status unknown, receive platinum-based doublet chemotherapy
Comparator	Test: No *EGFR* mutation test to determine *T790M* status Medicine: All patients receive platinum-based doublet chemotherapy
Outcomes	Test: Diagnostic accuracy of *EGFR T790M* mutation Medicine: 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; TKI = tyrosine kinase inhibitor; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
Source: Table 1.1, p18 of the main submission.

1.3 The proposal is for patients to undergo a rebiopsy to retrieve a tumour tissue sample at the point of progression on or after TKI treatment. This sample would then be used for *EGFR T790M* mutation testing, to determine eligibility for osimertinib. Those unable to undergo a rebiopsy, or who are *T790M* mutation negative, would receive platinum-based doublet chemotherapy.

1.4 The listing of osimertinib will displace platinum-based chemotherapy to a further line setting.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with 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

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Locally advanced (Stage IIIB) or metastatic (Stage IV)
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer
Treatment phase:	Initial
Restriction Level / Method:	☐Restricted benefit ☒*Authority Required - In Writing* ☒Authority Required - Telephone ☐Authority Required - Emergency ☒*Authority Required - Electronic* ☐Streamlined
Treatment criteria:	~~The treatment must be as monotherapy~~ ~~AND~~ ~~Patient must have received previous treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)~~
Clinical criteria:	*The treatment must be as monotherapy,* *AND* *Patient must have progressive disease following treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).*
Population criteria:	Patient must have evidence of a *T790M* mutation of the *EGFR* gene *in tumour tissue material* following progression on or after an EGFR TKI.
Administrative Advice	*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)		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Severity:	Locally advanced (Stage IIIB) or metastatic (Stage IV)
Condition:	Non-small cell lung cancer (NSCLC)
PBS Indication:	Locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer
Treatment phase:	Continuing
Restriction Level / Method:	☐Restricted benefit ☒*Authority Required - In Writing* ☒*Authority Required - Telephone* ☐Authority Required - Emergency ☒*Authority Required - Electronic* ☒~~Streamlined~~
Treatment criteria:	~~The treatment must be as monotherapy~~ ~~AND~~ ~~Patient must have previously been issued with an authority prescription for this drug~~
Clinical criteria:	*The treatment must be as monotherapy,* *AND* *Patient must have previously received PBS-subsidised treatment with this drug for this condition,* *AND* Patient must not have progressive disease *following PBS-subsidised treatment with this drug for this condition.*
Administrative Advice	*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)		

Category / Program	*GENERAL – General Schedule (Code GE)*
Prescriber type:	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *Midwives*
Severity:	*Locally advanced (Stage IIIB) or metastatic (Stage IV)*
Condition:	*Non-small cell lung cancer (NSCLC)*
PBS Indication:	*Locally advanced (Stage IIIB) or metastatic (Stage IV) non-small cell lung cancer*
Treatment phase:	*Grandfathering*
Restriction Level / Method:	☐ *Restricted benefit* ☒ *Authority Required - In Writing* ☒ *Authority Required - Telephone* ☐ *Authority Required - Emergency* ☒ *Authority Required - Electronic* ☐ *Streamlined*
Clinical criteria:	*Patient must have previously received non-PBS subsidised treatment with this drug for this condition prior to [listing date],* *AND* *The treatment must be as monotherapy,* *AND* *Patient must have progressive disease following treatment with an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI).* *AND* *Patient must not have progressive disease following treatment with this drug for this condition.*
Population criteria:	*Patient must have evidence of a T790M mutation of the EGFR gene in tumour tissue following progression on or after an EGFR TKI.*
Prescribing Instructions	*A patient may qualify for PBS-subsidised treatment under this restriction once only.*
Administrative Advice	*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.*

2.2 Osimertinib is an orally administered TKI that is a selective and irreversible inhibitor of *EGFR*s harbouring single (*L858R* or *del746-750*) or double (*L858R/T790M* or *del746-750/T790M*) mutations.

2.3 Establishing positive *EGFR T790M* mutation status after failure to prior first-line TKI therapy is necessary to be eligible for treatment with osimertinib.

- In the MBS item descriptor, the submission proposed use of a tumour tissue rebiopsy to determine T790M positivity whereas the approved osimertinib PI proposes the use of testing based on either tumour tissue or plasma;
- the ESCs noted that the proposed PBS restriction did not specify the type of sample;
- the ESCs considered that this was a significant issue, as some patients could elect to pay for plasma-based testing to avoid rebiopsy and still be eligible for osimertinib according to the proposed restriction;
- however, the ESCs considered that the lack of evidence regarding the comparative effectiveness of osimertinib in patients with T790M mutations in plasma, and the biologically plausible variation in prognostic value of test results

from these two sources of test samples, would mean that a new submission should be required to determine eligibility for osimertinib on the basis of plasma testing for these mutations; and

- the ESCs therefore advised that the wording of any PBS restriction should specify use of tumour tissue material to determine *T790M* positivity to be consistent with the primary basis of patient selection in the AURA3 trial, consistent with the current PBS restrictions for TKIs such as erlotinib and gefitinib.

2.4 The recommended dose of osimertinib is 80 mg once a day until disease progression or unacceptable toxicity. If a dose reduction is necessary due to toxicity or safety, then the dose of osimertinib should be reduced to 40 mg taken once daily. This is consistent with the approved Therapeutic Goods Administration (TGA) Product Information (PI) for osimertinib.

2.5 The submission proposed a Special Pricing Arrangement (SPA). The proposed effective price for osimertinib represents a [redacted]% rebate on the published dispensed price for maximum quantity.

2.6 The requested listing allows patients with any performance status (PS) to receive treatment with osimertinib, whereas the majority of the osimertinib studies only included patients with a World Health Organisation (WHO) PS of 0 or 1.

2.7 The proposed restriction does not exclude use of osimertinib after platinum-based chemotherapy.

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".

3.2 The ESCs noted that the approved TGA indication does not specify that osimertinib must be used in patients with progressive disease after prior TKI therapy. The proposed PBS restriction is for patients who have progressed on or after EGFR TKI therapy. The ESCs advised that, although this was reasonable because the evidence on osimertinib provided in the submission was for patients who have progressed on prior TKI therapies, there would be a significant risk of leakage into first-line therapy.

Previous PBAC consideration

3.3 This is the first PBAC submission for osimertinib.

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 biomarker is the *EGFR T790M* mutation, which is a point mutation that results in the substitution of threonine (T) with methionine (M) at amino acid position 790 in the kinase domain of exon 20 of the *EGFR* gene. This mutation increases the binding affinity of *EGFR* for adenosine triphosphate (ATP), which therefore reduces the binding rate of ATP competitive TKIs and restores enzymatic activity. *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. For this reason, it is important that a new sample is collected on progression for the purposes of *EGFR T790M* mutation status to determine eligibility for osimertinib. Overall, *EGFR T790M* mutations are detected in approximately 60%[1] of patients with locally advanced or metastatic NSCLC who have progressed on or after treatment with an EGFR TKI.

4.3 The submission requested listing of osimertinib for *T790M* mutation positive patients who have failed first-line EGFR TKIs. Second-line treatment most commonly consists of platinum-based doublet chemotherapy, the nominated main comparator in the submission.

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

[1] 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

5 Comparator

5.1 The submission nominated no testing for *EGFR T790M* mutations and all patients treated with platinum-based doublet chemotherapy as the main comparator. This is reasonable. The ESCs considered that the nominated comparators for both *EGFR T790M* mutation testing and osimertinib treatment were appropriate.

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, a clinician presented data highlighting the benefits of osimertinib treatment in *EGFR T790M* mutation positive NSCLC. The clinician discussed the benefits of osimertinib treatment over chemotherapy, particularly in patients who had central nervous system (CNS) metastases at baseline, and addressed other matters in response to the Committee's questions. The PBAC considered that the sponsor hearing was informative as it provided a clinical perspective on the treatment algorithm of EGFR mutation positive NSCLC in Australia.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (19), heath professional (1) and organisations (1) 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.

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 for EGFR mutation positive NSCLC in Australia.

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)[2], based on a comparison against platinum-based chemotherapy and pemetrexed treatment.

Clinical trials

6.5 The submission presented clinical evidence to demonstrate that targeting patients with the *T790M* mutation with osimertinib will improve their overall survival, compared to no testing and treatment with platinum-based doublet chemotherapy.

[2] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

Table 2: Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied	Overall risk of bias in clinical trials
Accuracy and performance of the test (analytical validity)	Concordance studies between evidentiary standard and other forms of *EGFR* mutation testing [a]	☒ k=3 n=833	Low to moderate risk of bias
Prognostic evidence	Comparison of outcomes in patients with and without *T790M* mutations (based on plasma) who receive the chemotherapy + placebo	☒ k=1 n=120	High risk of bias due to use of plasma-based rather than tumour tissue-based test
Predictive evidence	Comparison of outcomes in patients with and without *T790M* mutations (based on tumour tissue) who receive osimertinib	☒ k=1 n=244	High risk of bias for interpretation of predictive validity, as this is based on a naïve indirect comparison with the prognostic evidence
Change in patient management	Not supplied	☐ k=0" n=NA	
Treatment effectiveness Treatment effect (enriched)	AURA3 [b] was a head-to-head trial comparing osimertinib with platinum-based chemotherapy in tumour *T790M* positive patients. However, due to treatment switching in AURA3, the submission used a naive indirect comparison [c] between 2 single-arm osimertinib studies and a single platinum-based chemotherapy arm from the IMPRESS trial.	☒ k^b=1 n= 419 ☒ k^c=3 n= 190	[b] Direct comparison at low risk of bias for PFS, although high risk of bias for OS [c] Naïve indirect comparison at high risk of bias

[a] reference standard not available; [b] direct comparison; [c] indirect naïve comparison; k=number of studies, n=number of patients.
Source: Complied during the evaluation.

6.6 Data available for the linked evidence components are outlined in Table 3.

6.7 Gaps in the evidence include comparative treatment effectiveness in patients who are *T790M* mutation negative. The benefit of selective osimertinib treatment has not been assessed i.e. treatment based on *EGFR* mutation testing, rather than non-selective treatment. The submitted evidence does not allow a distinction between prognostic and predictive effects.

Table 3: Data availability to inform comparisons

Proposed test vs no test	-	
Proposed test vs alternative test	AURA1A/1B, AURA2, Hor et al (2016)	
	Osimertinib	**Platinum-based doublet chemotherapy**
Biomarker test positive	AURA1B (*T790M* mutation status based on tumour tissue) AURA3 (*T790M* mutation status based on tumour tissue) AURA1C and AURA2 (*T790M* mutation status based on tumour tissue)	IMPRESS (*T790M* mutation status based on plasma) AURA3 (*T790M* mutation status based on tumour tissue)
Biomarker test negative	AURA1B (*T790M* mutation status based on tumour tissue)	IMPRESS (*T790M* mutation status based on plasma)

Source: Complied during the evaluation.

6.8 Populations selected by positive results in plasma and tumour tissue had different spectrums of disease. The findings from different components of the linked evidence approach were therefore not transferrable.

6.9 There was a high risk of bias associated with the included evidence (Table 4).

Comparative effectiveness

6.10 Details of the treatment trials presented in the submission are provided in the table below.

Table 4: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Study report date/Publication citation
Direct randomised trial of osimertinib versus platinum-based chemotherapy		
AURA3	Internal study reports 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).	[redacted]
	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, [redacted].	[redacted]
	[redacted]	[redacted]
	Publications Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in *EGFR T790M*-positive lung cancer.	New England Journal of Medicine 2017; 376 (7):629-640
	Papadimitrakopoulou et al. Randomized Phase III study of osimertinib vs platinum-pemetrexed for *EGFR T790M*-positive advanced NSCLC (AURA3).	Journal of Thoracic Oncology 2017; 12(1):S5-S6.
	Wu et al (2017). Osimertinib vs platinum-pemetrexed for *T790M*-mutation positive advanced NSCLC (AURA3): Plasma ctDNA analysis.	Journal of Thoracic Oncology 2017;12(1):S386.
Single-arm non-comparative studies used for the naïve indirect comparison presented in the submission		
OSIMERTINIB		
AURA2	Internal study report A Phase II, open-label, single-arm study to assess the safety and efficacy of osimertinib in patients with locally advanced/metastatic non-small cell lung cancer who.se disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy and whose tumours are epidermal growth factor receptor mutation and *T790M* mutation positive (AURA2). Clinical Study Report D5160C00002. Edition 3. [redacted]	[redacted]
	Publications Goss et al. Osimertinib for pre-treated *EGFR* Thr790Met-positive advanced non-small cell lung cancer (AURA2): a multicentre, open-label, single-arm, Phase II study.	The Lancet Oncology 2016; 17(12):1643-1652
	Mitsudomi et al. AZD9291 in pre-treated *T790M* positive advanced NSCLC:	Journal of Thoracic Oncology

Trial ID	Protocol title/ Publication title	Study report date/Publication citation
	AURA2 Phase II study.	2015; 10(9):S320
	Rudell et al. The impact of osimertinib on function and health status for patients with *EGFR* mutation-positive advanced non-small cell lung cancer.	Journal of Clinical Oncology 2016; 34.
	Bodnar et al. Health state utility measured by EQ-5D-5L for *EGFR* mutant *T790M* NSCLC patients treated with osimertinib.	Annals of Oncology 2016; 27 (Suppl. 6):1041P
AURA1C	Internal study report A Phase II, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of ascending doses of osimertinib in patients with advanced non-small cell lung cancer who have progressed following prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor agent [AURA Phase II Extension (AURA1C)]. Clinical Study Report D5160C00001. Edition 3. [redacted]	[redacted]
	Publications Yang et al. Osimertinib in pre-treated *T790M*-positive advanced non-small cell lung cancer: AURA Study Phase II Extension Component.	Journal of Clinical Oncology 2017; 35(12):1288-1296
	Yang et al. AZD9291 in pre-treated *T790M* positive advanced non-small cell lung cancer (NSCLC): AURA study Phase II extension cohort.	Journal of Thoracic Oncology 2015; 10(9):S319.
AURA Pooled (AURA1C + AURA2)	Internal study report Osimertinib D5160C00001 and D5160C00002 Integrated summary of pooled clinical efficacy data for osimertinib for the treatment of patients with locally advanced or metastatic *EGFR T790M* mutation positive non-small cell lung cancer (NSCLC) who have progressed on or after *EGFR*-TKI therapy. [redacted]	[redacted]
	Publications Yang et al. Osimertinib (AZD9291) in pre-treated pts with *T790M*-positive advanced NSCLC: Updated Phase 1 (P1) and pooled Phase II (P2) results.	Journal of Thoracic Oncology 2016; 11(4): S152-S153
	Goss et al. AZD9291 in pre-treated patients with *T790M* positive advanced non-small cell lung cancer (NSCLC): Pooled analysis from two Phase II studies.	European Journal of Cancer 2015; 51: S640
	Ahn et al. AZD9291 activity in patients with *EGFR*-mutant advanced non-small cell lung cancer (NSCLC) and brain metastases: Data from Phase II studies.	European Journal of Cancer 2015; 51: S625-S626
	Ryden et al. Patient experience of symptoms and side effects when treated with AZD9291 for advanced non-small cell lung cancer: A qualitative interview sub-study.	European Journal of Cancer 2015; 51: S221
	Ryden et al. Patient-reported symptom response and impact of treatment with AZD9291 for advanced non-small cell lung cancer.	European Journal of Cancer 2015; 51: S606
	Jenkins et al. Plasma Circulating tumour DNA (ctDNA) analysis for detection of *EGFR T790M* mutation in patients (pts) with *EGFR* mutation-positive advanced non-small cell lung cancer (aNSCLC).	Journal of Thoracic Oncology 2016; 11(4): S153-S154
	Goss et al. Central Nervous System (CNS) response to osimertinib in patients with *T790M*-positive advanced NSCLC: Pooled data from two Phase II trials..	Journal of Thoracic Oncology 2017; 12(1):S440-S441
	Novello et al. Analysis of patient-reported symptom response with osimertinib (AZD9291) treatment for advanced non-small cell lung cancer.	Journal of Thoracic Oncology 2017; 12(1):S1238-S1239
PLATINUM-BASED CHEMOTHERAPY (Chemotherapy alone single arm sourced from the randomised controlled trial IMPRESS)		

Trial ID	Protocol title/ Publication title	Study report date/Publication citation
IMPRESS	Internal study report A Phase III randomised, double-blind, placebo-controlled, parallel, multicentre study to assess the efficacy and safety of continuing gefitinib 250mg in addition to chemotherapy versus chemotherapy alone in patients who have epidermal growth factor receptor (*EGFR*) mutation positive locally advanced or metastatic non-small cell lung cancer (NSCLC) and have progressed on first-line gefitinib (IMPRESS). Clinical Study Report D791LC00001: Edition 1	[redacted]
	Publications Soria J-C, Wu Y-L, Nakagawa K, Kim S-W, et al. Gefitinib plus chemotherapy versus placebo plus chemotherapy in *EGFR*-mutation-positive non-small-cell lung cancer after progression on first-line gefitinib (IMPRESS): a Phase III randomised trial.	The Lancet Oncology 2015; 16(8):990-998.
	Nakagawa K, et al. Gefitinib / chemotherapy vs chemotherapy in epidermal growth factor receptor (*EGFR*) mutation-positive NSCLC resistant to first-line gefitinib: IMPRESS *T790M* subgroup analysis.	World Conference Lung Cancer. 2015

Source: Table 2-2, pp37-8 of the submission.

Table 5: Key features of the included evidence

Trial	N	Design/ Mean treatment duration	Patient population	Outcomes	Use in modelled evaluation
Osimertinib versus platinum-doublet chemotherapy					
AURA 3	419	R, OL Osimertinib arm: [redacted]; Chemotherapy arm: [redacted]	*T790M* mutation positive NSCLC patients who have failed prior EGFR TKI	PFS, response rate	PFS gains
Single-arm studies used in the indirect comparison					
Osimertinib					
AURA1C	61*	2nd-line subgroup of single arm, [redacted]	*T790M* mutation positive NSCLC patients who have failed prior EGFR TKI	OS, response rate	Not used
AURA2	68*	2nd-line subgroup of single arm, [redacted]	*T790M* mutation positive NSCLC patients who have failed prior EGFR TKI	OS, PFS	Not used
Pooled*	129*	Included AURA1C AND AURA2 sub-group analysis. Treatment duration not reported for pooled 2nd-line subgroup. All lines: 10.9 months	*T790M* mutation positive, (determined by tumour sample) NSCLC patients who have failed prior EGFR TKI	PFS, OS	Survival gains
Chemotherapy					
IMPRESS	61	*T790M* positive subgroup of a single arm from an RCT, exploratory biomarker analysis Chemotherapy arm: [redacted]	The subgroup of *T790M* mutation positive (determined by plasma-based testing) patients who were treated with platinum-chemotherapy after failure to prior EGFR TKI	PFS, OS	Survival gains

*only subgroups of patients who received osimertinib as a second-line treatment in AURA1C and AURA2 were included in indirect comparison, the total numbers of subjects in AURA1C and AURA2 were 201 and 210 respectively.

[redacted]

AURA single-arm studies – [redacted].

IMPRESS: Clinical Study Report, OS Addendum p16 reported the median duration of follow-up as "504 months" in the chemotherapy only

group which does not appear plausible.
DB = double blind, R = randomised; OL=open label; OS=overall survival; PFS=progression-free survival; *EGFR* = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor; NSCLC = non-small cell lung cancer; RCT = randomised controlled trial.
Source: compiled during the evaluation.

6.11 The submission noted that overall survival (OS) data from AURA3 remained immature [redacted] and [redacted]% of patients randomised to chemotherapy had switched to osimertinib upon progression. The submission, therefore, presented a naïve indirect comparison of osimertinib versus platinum-chemotherapy using subgroups of AURA1C and AURA2 that have been pooled and compared to the chemotherapy arm of the IMPRESS trial.

6.12 A summary of the head-to-head randomised trial results, conditional on biomarker status, is provided in the table below.

Table 6: AURA3: PFS and OS results for *T790M* mutation positive population treated with either osimertinib or platinum-based chemotherapy

Endpoint	Osimertinib	Chemotherapy	Hazard ratio (95% CI)	p-value
	N=279	N=140		
PFS[a]				
Events, (progression or death) n (%)	140/279 (50.2)	110/140 (78.6)	0.30 (0.23, 0.41)	<0.001
Median, months (95% CI)[b]	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)		
% of patients progression free by time point (95% CI)[b]				
6 months	68.8 (62.9, 74.0)	36.9 (28.5, 45.3)		
12 months	44.0 (36.9, 50.9)	9.8 (4.9, 16.9)		
OS[b]				
Events, (death) n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median, months (95% CI)[b]	[redacted]	[redacted]		
% survival by time point (95% CI)[b]				
6 months	[redacted]	[redacted]		
12 months	[redacted]	[redacted]		

[a] Results are presented for the analysis of PFS based on investigator assessment and medians calculated using the Kaplan-Meier technique. The AURA3 CSR DCO1 (Table 11.2.1.3.1) reported that the median follow-up for PFS was 8.4 months for osimertinib and 5.5 months for chemotherapy
[b] [redacted]

CI = confidence interval; PFS = progression-free survival; OS = overall survival; NC = not reached/not calculated.
Source: Table 2-17, p72 of the main submission.

6.13 No adjustment for treatment switching in the AURA3 trial was presented in the submission.

- The Pre-Sub-Committee Response (PSCR) (p3) claimed that a naïve indirect comparison was considered more appropriate than a statistical adjustment for treatment switching, as:
  - by the time of the interim analysis, [redacted]% of the chemotherapy arm of AURA3 had switched to osimertinib after disease progression, substantially confounding OS results;

- the primary analysis cut-off had not been reached. OS data from AURA3 were still immature, [redacted]; and
- adjustment methods that involve subsets of patients or events would reduce the sample size even further. In this case, there would be too few patients left in the analysis for switching-adjustment methods to be meaningful.

- The ESCs acknowledged the limitations cited by the PSCR, but maintained that the AURA3 trial represented the most relevant evidence and therefore more mature data on the ITT population of this trial would have been preferred to the naive indirect comparison presented in the submission.

6.14 Further, there was a higher proportion of patients with Asian background in AURA3 (65%) compared to Australian clinical practice (23%). In subgroup analyses of the AURA3 trial, the point estimate of the hazard ratio (HR) for progression-free survival (PFS) was more favourable for osimertinib compared to chemotherapy in Asians (HR 0.32 (95% CI: 0.24, 0.44)) than that in non-Asians (HR 0.48 (95% CI: 0.32, 0.75)). The ESCs considered that, although this was likely to have reduced the difference in comparative benefit with osimertinib treatment, it did not rule out a PFS benefit with osimertinib treatment entirely.

6.15 The results of the naïve indirect comparison of osimertinib versus platinum-based chemotherapy are presented below.

Table 7: Naïve comparison of efficacy results for osimertinib versus platinum-doublet chemotherapy as second-line treatment in patients with *EGFR T790M* mutation positive NSCLC

Endpoint	Osimertinib, AURA1C and AURA2 pooled; *T790M* positive determined prospectively by tumour rebiopsy, N=129	IMPRESS Platinum-doublet chemotherapy; *T790M* positive determined retrospectively by plasma-based samples, N=61
PFS		
Events, (progression or death) n (%)	[redacted]	51 (83.6)
Median, months (95% CI)	[redacted]	5.3
OS		
Events (deaths), n (%)	[redacted]	[redacted]
Median, months (95% CI)	[redacted]	[redacted]
ORR		
ORR, % , (95% CI)	[redacted]	39.3
DCR		
DCR, %, (95% CI)	[redacted]	77.0

Attachment 9 to the main submission did not present 95% CI for the IMPRESS chemotherapy alone treatment arm.
AURA single-arm studies – [redacted].
IMPRESS: Clinical Study Report, OS Addendum p16 reported the median duration of follow-up as "[redacted] months" in the chemotherapy only group which does not appear plausible.
CI = confidence interval; CR = complete response; DCR = disease control rate; NC = not reached/calculable; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST = Response Evaluation Criteria In Solid Tumours; SD = standard deviation
Source: Table 15, p21 of Attachment 9 to the main submission.

6.16 The ESCs noted that in *EGFR T790M* mutation positive advanced NSCLC patients, the median OS had not been reached in the osimertinib single-arm studies at the time of

interim analysis ([redacted]). The PSCR (p2) acknowledged the immature nature of the OS data presented in the submission, and presented further survival data that showed that the median OS for AURA1C and AURA2 (pooled) had been reached at 26.8 months and 73% of patients (301/411) had experienced disease progression.

6.17 Without a common reference, prognostic differences across the osimertinib and chemotherapy treatment arms could not be differentiated from the direct treatment effect. Importantly, *T790M* mutation positivity was not determined using comparable methods in the AURA studies and IMPRESS trial. The populations included in the naïve indirect comparison may not be similar in terms of prognostic factors. Chemotherapy-treated *T790M* positive patients from IMPRESS were more likely to have had a poorer prognosis than osimertinib treated *T790M* positive patients from the AURA studies. Therefore, the results of the indirect comparison were likely to be biased in favour of osimertinib.

6.18 The ESCs noted that, in the IMPRESS chemotherapy arm, *T790M* positive status was determined in an exploratory manner via plasma-based testing[3]. *T790M* positive status based on plasma testing is likely to be reflective of patients with a high tumour burden and distant metastases (shedders) who are unable to have a tumour rebiopsy, thus potentially identifying a group of patients with a poor prognosis. In contrast, *T790M* positive status was prospectively determined via tumour rebiopsy in the osimertinib single-arm studies. Identifying patients in this manner is unlikely to select only patients with a high tumour burden. Although the PSCR (p1) contended that a comparison of the chemotherapy arm results from the IMPRESS and AURA3 studies suggested a similarity in efficacy outcomes, and hence did not support the suggestion of a differing prognostic effect for patients in the IMPRESS trial with a *T790M* mutation in their plasma, the ESCs considered that the selection bias arising from relying on plasma-based testing was likely to favour osimertinib.

6.19 Overall, the ESCs advised that the magnitude of benefit, if any, of osimertinib treatment was confounded by the immaturity of the survival data and the biases in the indirect comparison.

Comparative harms

6.20 A summary of adverse events (AEs) from AURA3 is presented below.

[3] Jenkins, S, Yang, JC, Ramalingam, SS, Yu, K, Patel, S, Weston, S, Hodge, R, Cantarini, M, Janne, PA, Mitsudomi, T & Goss, GD 2017, 'Plasma ctDNA Analysis for Detection of the *EGFR* T790M Mutation in Patients with Advanced Non-Small Cell Lung Cancer', *J Thorac Oncol*, vol. 12, no. 7, Jul, pp. 1061-1070.

Table 8: AURA3 summary of adverse events

AE category [a]	Osimertinib N=279	Chemotherapy N=136
Any AE, n (%)	273 (97.8)	135 (99.3)
Any AE possibly related to study treatment [b]	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 [b]	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 [b]	2 (0.7)	1 (0.7)
Any SAE	65 (23.3)	35 (25.7)
Any SAE, possibly related to study treatment [b]	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 [b]	12 (4.3)	13 (9.6)

[a] 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.
[b] 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 2-19, p80 of the main submission.

6.21 The safety profile of osimertinib differs from chemotherapy and both are well established. Skin, nail and gastrointestinal effects were more prominent with osimertinib and there were more haematological events associated with platinum-based chemotherapy. AEs with a higher incidence in the osimertinib arm than in the chemotherapy arm included diarrhoea (41% vs. 11%), paronychia (19% vs. 2%) and dermatitis (14% vs. 2%), consistent with the known class effects for EGFR TKIs (e.g. gefitinib and erlotinib). AEs with a higher frequency in the chemotherapy arm than in the osimertinib arm included nausea (49% vs. 20%), anaemia (30% vs. 8%), neutropenia (13% vs. 4%), decreased platelet count (15% vs. 5%), and asthenia (15% vs. 7%). In AURA3, interstitial lung disease (ILD) was reported in 4.3% of patients who received treatment with osimertinib, compared to 1.5% of those who received chemotherapy. The Periodic Benefit-Risk Evaluation Report, provided in Attachment 7 to the main submission, noted that ILD was an important identified risk associated with osimertinib and that cases of ILD have been reported in 3.2% (22/690) of patients who received treatment with osimertinib in Phase II and Phase III clinical studies.

6.22 For the majority of patients, listing of osimertinib would displace, rather than substitute, platinum-doublet chemotherapy to a later line of treatment. For these patients, chemotherapy-related AEs would be delayed, rather than totally avoided. To inform the comparative safety of osimertinib, relative to platinum-based chemotherapy, safety data from the direct AURA3 trial should be considered more relevant than the indirect safety analyses.

Benefits and harms

6.23 A summary of the comparative benefits and harms for osimertinib versus platinum-based chemotherapy is presented in the table below. The table is based on the key head-to-head trial AURA3. Benefits and harms from the naïve indirect comparison between the single-arm studies could not be meaningfully interpreted. Interpretation of the benefits and harms from AURA3 should consider the immaturity of the OS data and treatment switching from chemotherapy to osimertinib upon disease progression.

Table 9: AURA3: Summary of comparative benefits and harms for osimertinib and platinum-based chemotherapy

Benefits				
	Osimertinib N = 279 Mean duration of exposure: 11.1 months	**Chemotherapy N = 140 Mean duration of exposure: 5.2 months**	**Absolute difference**	**HR (95% CI)**
Overall survival				
Deaths, n (%) % surviving at 12 month - time point (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS median months (95% CI)	[redacted]	[redacted]	[redacted]	
RECIST-defined PFS (Investigator confirmed by independent review)				
Progressed, n (%)	140 (50.2)	110 (78.6)	29%	0.30 (023, 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				
	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)

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 submission.

6.24 On the basis of the AURA3 trial, treating *T790M* tumour positive advanced NSCLC patients (after failure of TKI therapy) with osimertinib for an average period of 11 months:

- 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.

Interpretation of the clinical evidence

6.25 The submission claimed that osimertinib was superior to platinum-based doublet chemotherapy in terms of effectiveness and safety, in the proposed *T790M* mutation positive NSCLC population after failure of first-line TKIs.

6.26 The ESCs considered that:

- the PFS data indicated there was a significant improvement in median PFS of approximately 6 months associated with osimertinib treatment compared with chemotherapy (median follow-up for PFS was approximately 8 months for osimertinib and 6 months for chemotherapy); and
- the OS data presented were potentially confounded by patients switching on progression from chemotherapy to osimertinib, and were insufficiently mature [redacted] cut-off date to be meaningful [redacted].

6.27 Despite the PSCR's arguments (see paragraph 6.13), the ESCs advised that the naïve indirect comparison evidence was not informative in estimating the magnitude of comparative effectiveness of osimertinib treatment compared with chemotherapy.

6.28 The pre-PBAC response (p2) stated that median OS for AURA Pooled had been reached (26.8 months), and claimed that the modelled OS curve was identical to the longer-term OS data for second-line patients in AURA Pooled. The pre-PBAC response (p3) also maintained that a naïve indirect comparison of AURA Pooled and IMPRESS was more appropriate than a statistical adjustment for treatment switching in AURA3, citing (i) the immaturity of OS data at the interim analysis of AURA3.; (ii) [redacted]% of patients in the chemotherapy arm of AURA3 had switched to osimertinib after disease progression; and (iii) similar demographics and characteristics of patients enrolled in AURA3, AURA Pooled and IMPRESS, minimising any issue of applicability.

6.29 The PBAC advised that the less scientifically rigorous naive indirect comparison presented in the submission increased the uncertainty around quantifying the incremental benefit of osimertinib. By comparison, the AURA3 trial represented a more scientifically rigorous source of evidence and therefore more mature data from this trial based on an ITT analysis, or possibly based on a well-justified adjustment for treatment switching, would have been preferred.

6.30 Further, the PBAC considered that the OS data was immature in all of the evidence presented in the submission to support its claim of osimertinib's superior OS effect over chemotherapy. The PBAC advised that the longer follow-up results from the AURA Pooled studies (subsequently presented at a conference and referred to in the PSCR and pre-PBAC response) did not provide a more convincing basis to accept any estimate of incremental OS benefit with osimertinib.

6.31 The PBAC advised that, while the submission's claim of superiority compared with chemotherapy was reasonable in terms of response rates, PFS and safety-based outcomes on the results of the AURA3 trial, the magnitude of OS benefit with osimertinib treatment, if any, remained inconclusive due to the immaturity of the survival data presented in the submission and PSCR, and a lack of adjusted analyses to account for treatment switching.

Economic analysis

6.32 The submission presented a modelled cost-utility analysis, using the randomised trial (AURA3, which compared osimertinib and chemotherapy in a population of patients with *T790M*+ NSCLC, after progression following EGFR TKI) to inform PFS, and the naïve indirect comparison of nonrandomised studies (AURA Pooled and IMPRESS) to inform OS. A summary of the structure and rationale for the economic model is presented in Table 10.

Table 10: Summary of model structure and rationale

Component	Description	Justification/comments
Time horizon	10 years in the model base case versus [redacted] months in the AURA3 trial	The submission selected the time horizon based on the modelled time by which the large majority of patients had died. This may not be reasonable. The PBAC has previously accepted a 5-year time horizon for first-line treatments of NSCLC (PBAC erlotinib and afatinib PSDs, July 2013) and osimertinib is proposed as a second-line treatment.
Outcomes	Life-years gained, quality-adjusted life-years gained	Reasonable
Methods used to generate results	Markov cohort expected value analysis.	Reasonable
Health states	Progression-free on treatment with osimertinib; Progression-free on treatment with platinum-based doublet (either in the second-line setting in patients not treated with osimertinib, or in the third-line setting in a proportion of osimertinib-treated patients); Progressing disease following chemotherapy (on BSC or salvage therapy for some); Death	The use of a four-health state model for patients who begin on second-line osimertinib was not adequately justified (i.e. was not clear why two separate progression-free health states were warranted for patients who start on osimertinib, and only one progression-free health state for patients who start on chemotherapy).
Utilities	Progression-free utilities: AURA3 Progressive disease: IMPRESS	This was reasonable however the progression-free utility was applied to the 'progression-free on or after chemotherapy' health state after disease progression on osimertinib. This was not justified however, had only a minor effect on the ICER. [a]
Cycle length	30 days	This was reasonable, however every cycle 1/12 of a QALY or LY was gained (which equates to 30.4 days), whereas technically, 30/365.25 of a LY or QALY should be gained per cycle.
Transition probabilities	• Data from patients prior to progression in the relevant treatment arms of AURA3 were used in *T790M*+ patients to inform the transitions from the progression-free health states. • Data from unprogressed patients in the control arms of IMPRESS were used in *T790M*– patients to inform the transitions from the progression-free health states. • Data from progressed patients in the second-line cohort of AURA Pooled were used to inform the transition from progressive disease	The use of supportive evidence (AURA Pooled and IMPRESS) when a direct trial (AURA3) was available was inadequately justified. Analyses based on the ITT results from AURA3 would be more informative, with adjustment for treatment switching considered in sensitivity analyses. The approaches used to estimate the transition probabilities in the model were inconsistent and selected by highly subjective visual inspection. Some transitions were informed by small

	to death after osimertinib treatment in *T790M+* patients. • Data from progressed patients in the control arm of IMPRESS were used to inform the transition from progressive disease to death after chemotherapy, by *T790M* status.	patient numbers and may lack precision. Constant transition probabilities, which favoured survival for patients who had received osimertinib, were used in the model beyond the study time horizons. This implied an ongoing treatment effect over the entire duration of the model, which was not justified.
Test parameters	PPV and NPV incorporated in a decision analytic which determines the treatments received by underlying *T790M* status.	Reasonable.
False positives/ negatives	The base case analysis assumed that the performance of the test in the trial would be replicated in practice. Sensitivity analyses were included in which: • False negative patients were assumed to forego benefit. • False positive patients were assumed to receive the same benefit from osimertinib treatment as if they had received chemotherapy (i.e. no net harm from osimertinib treatment).	The assumption in false positives was based on a naïve indirect comparison of single-arm studies (AURA1B *T790M-* on osimertinib v IMPRESS *T790M-* on chemotherapy). As there may be prognostic differences due to the different testing methods used in these studies, the conclusion that PFS is similar may not be reasonable and may not be consistent with the biological plausibility of targeted therapy.

[a] As 48% of patients who progress were estimated to transition to this health state after osimertinib treatment (based on a survey of 30 medical oncologists), and as time in this health state is short, the effect on incremental QALYs gained is small.
Source: Table 3-1, pp122-123 of the submission.

6.33 The key drivers of the economic model are presented in Table 11.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Osimertinib progressive disease → dead transition probabilities	Constant transition probabilities were used beyond cycle 8. Beyond this time point, an average of the remaining transitions (i.e. from cycle 8 to cycle 11) was used throughout the rest of the time horizon. The method used to select the time point from which to stop using the observed data and the type of data used to estimate the ongoing transition probabilities was based on visual inspection.	High, favours osimertinib
Cost of osimertinib	Submission applied a one-off treatment course cost based on the truncated mean duration of treatment observed in the trial (11 months), compared to a modelled mean duration in the 'progression-free on osimertinib' health state of approx. 13.6 months.	High, favours osimertinib
Osimertinib progression-free → progressive disease transition probabilities	Constant transition probabilities were used beyond cycle 9. Beyond this time point, an average of the transitions from cycle 4 to the remaining observations (cycle 16) was used throughout the rest of the time horizon. The method used to select the time point from which to stop using the observed data and the type of data used to estimate the ongoing transition probabilities was based on visual inspection.	Moderate, favours osimertinib
Time horizon	10 years	Moderate, favours osimertinib
Third-line nivolumab use after disease progression on chemotherapy	48% of those who progress on second-line chemotherapy based on a survey of 30 medical oncologists. This may be an overestimate due to the PBS listing requirement of a PS 0-1, however there are no data to refute or dispute this estimate.	Moderate, favours osimertinib

PS = performance status.
Source: compiled during the evaluation (reference sections/tables/spreadsheets within the submission)

6.34 A four-health state model was used for patients who began second-line treatment on osimertinib. The submission did not justify why two separate progression-free

health states were warranted for patients who started on osimertinib, compared to only one progression-free health state for patients who started on chemotherapy. There were also applicability issues regarding the transition probabilities and utility used in the chemotherapy health state after disease progression on osimertinib. The PSCR (p5) acknowledged that osimertinib would not substitute for chemotherapy, but rather displace it to a further treatment line, and that it was reasonable to assume some osimertinib patients (48% used in the analysis based on a survey of 30 medical oncologists) would still receive chemotherapy in the third-line setting. However, the PSCR stated that the structure of the model accounted for the possibility of an additional line of therapy in the osimertinib arm of the model, recognising that in these patients chemotherapy would be displaced to later line rather than replaced.

6.35 The ESCs further noted that the submission had not used standard survival analysis methods to extrapolate transition probabilities beyond the time point in the studies from which data became unstable. Constant transition probabilities were assumed beyond the study, which implied an ongoing treatment effect. As such, the ICER was highly sensitive to changes in the estimate of ongoing overall survival used.

6.36 The submission used a naïve indirect comparison of the pooled single-arm AURA1C and AURA2 studies with the IMPRESS study, rather than the direct AURA3 intention-to-treat (ITT) analysis ± adjustment for treatment switching) in the economic model.

6.37 Notwithstanding the PSCR's arguments in favour of using the pooled single-arm study data and against adjusting for treatment switching (see paragraph 6.13), the ESCs maintained that it would have been more informative to have used data from AURA3 to model the benefits of osimertinib, considering that:

- the event rate for the pooled analysis [redacted] the event rate observed in the AURA3 trial [redacted];
- to account for treatment switching, sensitivity analyses could have been conducted on the AURA3 chemotherapy arm data using different extrapolations to explore the impact of these assumptions on the modelled ICER;
- the difference in health outcomes resulting from the naïve indirect comparison of single-arm studies could potentially reflect both a treatment effect of osimertinib and a prognostic effect associated with the different testing methods used:
  - the PSCR (p4,5) attempted to address the concern regarding different testing methods via a reiteration of the PFS curves for the chemotherapy arms of IMPRESS (*T790M* positive patients only) and AURA3, implying an underlying assumption that PFS was a surrogate for OS;
  - however, the ESCs noted that the PBAC was previously concerned regarding the validity of this assumption (crizotinib Public Summary Document (PSD), November 2013 PBAC meeting) and it was not currently supported in the literature[4]. Additionally, no evidence was presented in the submission or the PSCR to support this claim; and

[4] Fiteni F, Westeel V, Bonnetain F. Surrogate endpoints for overall survival in lung cancer trials: a review. Expert Rev Anticancer Ther. 2017 May;17(5):447-54.

- use of a non-concurrent control (OS data from the chemotherapy only arm of IMPRESS) underestimated the survival gain associated with chemotherapy, biasing the model in favour of osimertinib.

6.38 The results of the stepped economic evaluation are presented in Table 12.

Table 12: Results of the stepped economic evaluation

Data	Costs			Health outcomes			ICER
	Proposed	Current	Increment	Proposed	Current	Increment	
Step 1 Setting: trial setting (*T790M+* only) Time horizon: 11 months [a]	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	**$[redacted] per additional responder**
Step 2 Setting: proposed MBS and PBS populations Time horizon: 10 years	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	**$[redacted] per LY gained**
Step 3 Study evidence transformed from LY to QALY	$[redacted]	$[redacted]	$[redacted]	[redacted]	[redacted]	[redacted]	**$[redacted] per QALY gained**

[a] Median time until loss of response for osimertinib
ORR = objective response rate; LY = life year; QALY = quality-adjusted life year.
Source: Table 3-32 and Table 3-33, p188 of the submission; Table 3-35, p189 of the submission and Table 3-37 and Table 3-38, p190 of the submission.

6.39 The incremental costs were likely an underestimate as the submission underestimated the cost of osimertinib treatment and may have overestimated the cost-offsets related to nivolumab use.

6.40 The cost of osimertinib used in the model might have been an underestimate, as it was based on the observed mean duration of treatment on osimertinib in the AURA3 study. This was a truncated mean, as [redacted]% of patients were still on osimertinib treatment at the latest data cut-off.

- The ESCs noted that, on applying the cost of osimertinib on a per cycle basis until disease progression consistent with the requested continuation criteria, the ICER increased from $75,000/QALY - $105,000/QALY to $75,000/QALY - $105,000/QALY (reflecting the extrapolated mean PFS for osimertinib of [redacted] months).
- Arguing that this approach did not account for dose interruptions or reductions due to tolerability, the PSCR (p3) and pre-PBAC response (p5) stated that, at the time of the submission, the actual mean treatment duration was [redacted] months versus a total median treatment duration of [redacted] months, resulting in a relativity of [redacted].
- The PSCR further stated that applying the cost of osimertinib on a per cycle basis to the model after factoring in this relativity of [redacted]% resulted in an ICER of $75,000/QALY - $105,000/QALY.
- The ESCs considered that this further dosage adjustment was uninformative, as it reinstated the observed truncated mean treatment duration without any extrapolation.

6.41 Nivolumab use in the chemotherapy-treated patients was the main driver of cost-offsets in the model. The model relied on a survey of 30 medical oncologists, who advised that, irrespective of the second-line treatment received, 52% of patients would receive BSC in the third-line setting. On this basis, 48% of patients were assumed to have other active therapies. For the osimertinib-treated arms of the model, this only had a small consequence on estimating utilities, because BSC comprised the only third-line option in this arm for costing purposes. However, for the chemotherapy arm, this also had a large cost-offset consequence because the 48% of patients were also assumed to be treated with third-line nivolumab. The PBAC noted that the osimertinib arm of the model did not allow nivolumab as fourth-line following progression on third-line chemotherapy.

6.42 As nivolumab was not used in the IMPRESS study after disease progression, the outcomes modelled did not capture the benefits associated with its use. Further, due to the performance status requirements (0-1) of the recent listing of nivolumab, the proportion of patients who would meet this criterion after disease progression on second-line chemotherapy was likely to have been overestimated. The PSCR (p6) argued that the outcomes of third-line use of nivolumab was implicitly captured in the model, as 54.5% of patients in the IMPRESS study received post-progression treatment with chemotherapy or novel agents, and the OS reported for IMPRESS (and used in the model) included gains associated with later line therapies including nivolumab.

6.43 While the majority of the incremental outcomes gained were accrued in the progression-free health state, some incremental outcomes were gained after disease progression (and so after treatment cessation of osimertinib). This was not reasonable, particularly given that these outcomes were informed by a naïve indirect comparison of single-arm studies.

6.44 As the incremental costs appear underestimated, and the incremental outcomes may have been overestimated, the ICER is likely to be an underestimate.

6.45 The time horizon used in the model was 10 years. As this was selected based on the extrapolated survival curves which were overly optimistic, the modelled benefit over 10 years was not reasonable. The PBAC has previously accepted a 5-year time horizon for first-line treatments of NSCLC (erlotinib and afatinib PSDs, July 2013 PBAC meeting). Given that the proposed place in therapy for osimertinib is in the second-line setting, and therefore at a later stage in disease, the base case time horizon was unrealistically long.

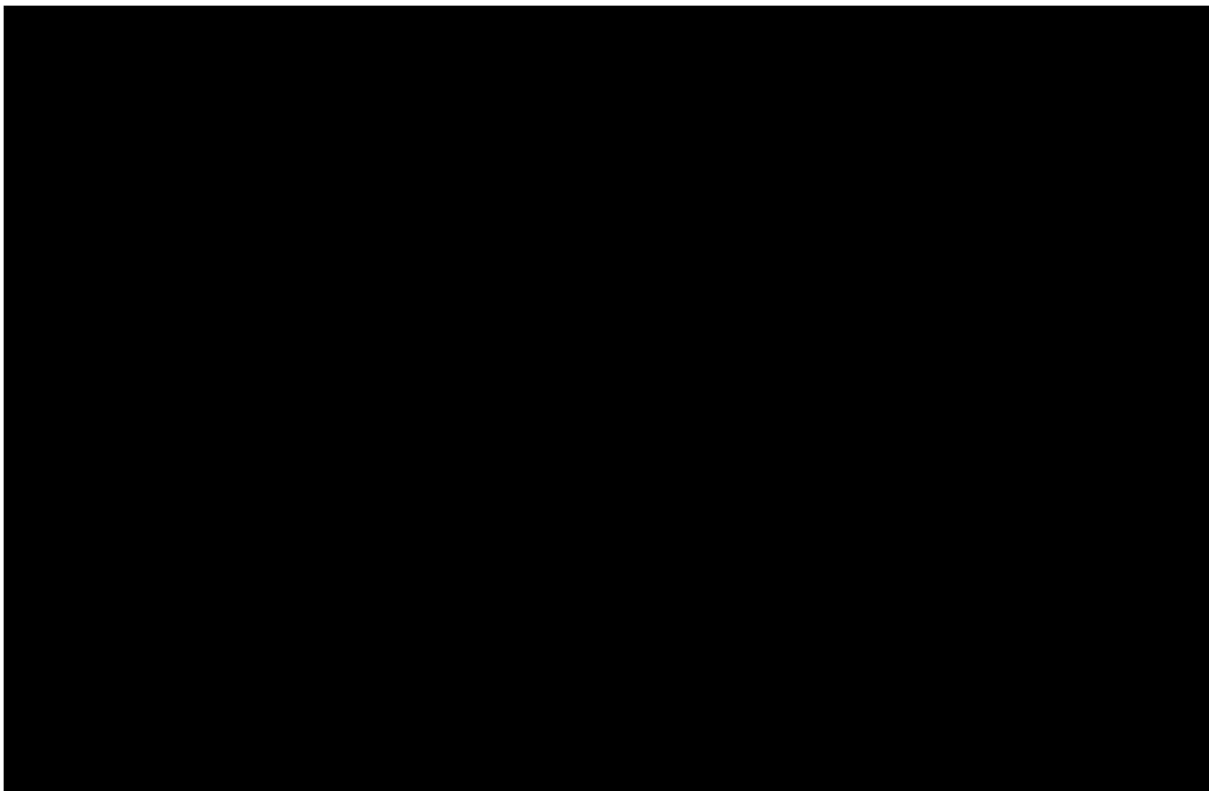
- the ESCs noted the PSCR's (p5) arguments stating that a 10 year time horizon was appropriate;
- the ESCs noted that most patients in the chemotherapy arm of the model had died by 5 years, demonstrating consistency with current expectations of prognosis for this population (as per PBAC's deliberations in relation to erlotinib and afatinib);
- the ESCs considered that, whilst it was reasonable to assume that the current expectations of prognosis in second-line advanced NSCLC would support a time

horizon of 5 years, it was possible that a breakthrough therapy could extend survival beyond this time; and

- overall, the ESCs advised that given the immaturity of the OS data from all of the AURA studies, it was currently not possible to confirm or refute the submission's choice of a 10 year time horizon.

6.46 A Markov trace of trial vs model results over the model time horizon is presented in Figure 1.

Figure 1: Markov trace of trial compared to modelled results over the model time horizon



Source: Figure 3-8, p184 of the submission.

6.47 An alternative scenario, conducted during the evaluation, exploring the cost-effectiveness of osimertinib without *T790M* testing is presented in Table 13.

Table 13: ICERs and considerations of various *T790M* testing and osimertinib funding scenarios

	ICER per QALY
Base case • MSAC funded test: testing on a new sample of tumour tissue from a patient who has progressed on or after treatment with an EGFR TKI • PBS restriction: Patient must have evidence of a *T790M* mutation of the *EGFR* gene following progression on or after EGFR TKI	$[redacted]
Scenario 1 [a] • No MSAC funded test • PBS restriction: All patients eligible for osimertinib after disease progression on or after EGFR TKI	$[redacted]

[a] This scenario maintains the submission's assumption that time in the progression-free health state in *T790M–* is the same on osimertinib as for chemotherapy. This assumption is highly uncertain as there is inadequate data on osimertinib used in *T790M-* patients. However, a different treatment course cost of osimertinib in *T790M–* is modelled (based on the time in the 'progression-free on osimertinib' health state, which is shorter than the duration in *T790M+* on osimertinib). Two corrections were additionally modelled: correcting the assumption

of additional life years gained in progressive disease in *T790M–* who received osimertinib and correcting the utility in progressive disease on third-line chemotherapy.
Source: Constructed during the evaluation from 'Model - osimertinib – NSCLC.trex'.

The redacted table shows ICERs in the range of $75,000/QALY - $105,000/QALY.

6.48 Results of the key univariate sensitivity analyses presented by the submission and additional analyses conducted during the evaluation are summarised in Table 14.

6.49 The submission did not present multivariate analyses. Three multivariate analyses were conducted during the evaluation; varying assumptions regarding the osimertinib transition probability from progression to dead, time horizon and applying the cost of osimertinib per cycle (see Table 14).

Table 14: Results of key sensitivity analyses

		Incremental costs	Incremental QALYs	ICER/ QALY	% change
	Base case	[redacted]	[redacted]	[redacted]	-
1	Osimertinib PD→D transition probability, using overall average transition probability ([redacted]) from cycle 0 onwards [a]	[redacted]	[redacted]	[redacted]	[redacted]
2	Cost of osimertinib applied in each cycle while in 'progression-free on osimertinib' health state	[redacted]	[redacted]	[redacted]	[redacted]
3	Osimertinib PD→D transition probability, using same ongoing transition probability as for chemotherapy transition (*T790M+*) ([redacted]) from cycle 7 onwards [b]	[redacted]	[redacted]	[redacted]	[redacted]
4	Osimertinib PF→PD transition probability, using transition probability from cycle 8 ([redacted]) onwards [c]	[redacted]	[redacted]	[redacted]	[redacted]
5	Time horizon, 5 years (truncated)	[redacted]	[redacted]	[redacted]	[redacted]
6	Osimertinib PD→D transition probability, using average ongoing transition probability of osimertinib and chemotherapy transitions (*T790M+*) ([redacted]) from cycle 7 onwards [b]	[redacted]	[redacted]	[redacted]	[redacted]
7	Third-line nivolumab use after disease progression on second-line chemotherapy in chemotherapy arm (18%) [d]	[redacted]	[redacted]	[redacted]	[redacted]
8	Discount rate is 0%	[redacted]	[redacted]	[redacted]	[redacted]
9	Osimertinib PF→PD transition probability, using overall average transition probability ([redacted]) from cycle 9 onwards [c]	[redacted]	[redacted]	[redacted]	[redacted]
10	Cost of pemetrexed as per prior to 1 April 2017 price cut	[redacted]	[redacted]	[redacted]	[redacted]
	Multivariate analyses				
	#2 AND #5	[redacted]	[redacted]	[redacted]	[redacted]
	#1 AND #2	[redacted]	[redacted]	[redacted]	[redacted]
	#1, #2 AND #5	[redacted]	[redacted]	[redacted]	[redacted]

[a] Base case value: varied until cycle 7, from then on [redacted]. The overall average per cycle probability may be more reasonable in the base case analysis as probabilities were implemented by cycle stage, rather than by time in the health state. As only 35% of patients had experienced a progression by the truncation time point (and so from then on an average transition probability was used) – the earlier (and higher transition probabilities) were not modelled in the majority of patients.
[b] Base case value: [redacted]
[c] Base case value: [redacted] (from cycle 9 onwards based on the average transitions from cycle 4 onwards)
[d] Base case value: 48%
D=dead health state; PD=progressive disease health state; PF=progression-free health state.
Source: Table 3-40, pp191-192 of the submission.

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

6.50 Acknowledging the uncertainty in the overall survival data, the pre-PBAC response (p3) proposed that the PBAC consider PBS listing via a managed entry scheme (MES), [redacted].

Medicine cost/patient/course: $[redacted].

6.51 The treatment course cost per *T790M*+ patient was $[redacted]. This was based on [redacted] months of osimertinib at the proposed effective DPMQ of $[redacted] per month. As described in Table 11, this was based on a truncated mean duration of treatment, as observed in the AURA3 study.

6.52 The cost of chemotherapy, including pemetrexed maintenance and administration, per *T790M*+ patient was $[redacted].

Estimated PBS & financial implications

6.53 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the PBS and MBS usage and financial implications. These were based on Australian Institute of Health and Welfare (AIHW) estimates, commissioned market research data and relevant literature.

6.54 A summary of the approach used to estimate the population eligible, and the uptake *T790M* testing and osimertinib treatment is presented in Table 15.

Table 15: Estimated use and financial implications of *T790M* testing and osimertinib listing

	2018	2019	2020	2021	2022	2023
Estimated extent of use of *T790M* testing						
Number of patients tested	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of patients likely to receive a positive test result (60%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated extent of use of osimertinib						
Grandfathered / prevalent patients	[redacted]	[redacted]				
Number of patients likely to be treated with proposed medicine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of the *T790M* testing to the MBS						
Cost of *T790M* testing	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	2018	2019	2020	2021	2022	2023
Copayments (revised) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to the MBS less copayments (revised) [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of osimertinib to the PBS/RPBS						
Cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for associated biopsies and reduction in chemotherapy administration to the MBS						
Increase in costs to the MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduction in costs to the MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to the MBS of associated services	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for reduction in use of chemotherapy, pemetrexed maintenance and nivolumab use						
Reduction to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised [e]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduction to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications						
Net cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net cost to health budget	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Revised	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Assuming 11 per patient as estimated by the submission.

[b] Revised to take into account the appropriate MBS benefit and patient contributions in the cost of testing. Estimates were based on 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.

[c] Revised to assume that in 65% of services, the 85% MBS benefit applies, and in 35% of services, the 75% MBS benefit applies.

[d] Revised 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; to assume 6 administrations per patient for nivolumab, as implied in Table 4-24, p208 of the submission, rather than 1 administration per patient as costed in the analysis; and to assume that in 8.5% of services, the 75% MBS benefit applies, and in the remainder of services, the 85% MBS benefit applies.

[e] Revised to account for, where applicable, the additional compound fee where compounding was undertaken at a TGA-licensed compounding site, as the PBAC have previously considered that the majority of chemotherapy preparations are compounded in these settings [PBAC bevacizumab PSD, November 2015]; to cost the most efficient combination of vials for the required average dose; and updated to reflect the EFC fees from 1 July, 2017.

Source: Table4-5, p198; Table 4-11, p201; Table 4-26, pp208-209; Table 4-20, p205; Table 4-21, p206; and Table 4-27, p208 of the submission.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $20 - $30 million per year.

6.55 The submission estimated that the number of patients eligible for testing each year would increase from less than 10,000 in Year 1 to less than 10,000 in Year 6 (see Table 15). Of those tested, 60% were assumed to be *T790M+* and would uptake osimertinib treatment. Grandfathered patients were accounted for in the estimates for Years 1 and 2. The estimated number of patients who would uptake treatment with osimertinib was less than 10,000 in Year 1 decreasing to less than 10,000 in Year 6 (see Table 15).

6.56 The submission estimated up to approximately less than 10,000 prescriptions of osimertinib dispensed per year, with a cumulative total of 10,000 – 50,000 prescriptions over the first 6 years (see Table 15).

6.57 The estimated total net cost to government was up to $20 - $30 million (revised: $20 - $30 million) per year, comprising a net cost of $20 - $30 million per year (revised: $20 - $30 million) to the PBS, and an estimate cost saving to the MBS of $ (revised: $) over the first 6 years (see Table 15).

6.58 Cost savings were claimed on the basis of a reduced number of patients being treated with chemotherapy (assumed to be carboplatin and gemcitabine, and associated pre-medication with palonosetron), pemetrexed maintenance and nivolumab use after disease progression on chemotherapy. While osimertinib would be expected to replace chemotherapy as second-line treatment, the submission assumed that some patients (48%) would still receive chemotherapy in the third-line setting (i.e. osimertinib would displace, rather than replace chemotherapy and pemetrexed maintenance). This was reasonable.

6.59 Pemetrexed maintenance was offset in the majority of patients in whom chemotherapy has been substituted. The proportion offset (73%) was not consistent with the survey data presented in the submission (53%). Unlike the AURA3 trial, pemetrexed maintenance therapy was not allowed in the IMPRESS trial.

6.60 The costs to the PBS might have been underestimated as the number of packs per patients was based on the truncated mean duration of treatment from the AURA3 study. A sensitivity analysis was conducted based on the extrapolated mean duration of treatment (Table 16).

Table 16: Sensitivity analysis based on the extrapolated mean duration of treatment

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Net cost to the PBS (revised)						
Assuming packs of osimertinib per patient [a]						

[a] Base case estimate: packs per patient. Alternative analysis was based on the average time in the 'progression-free on osimetinib' health state in the economic evaluation.

Source: Compiled during the evaluation using the 'Tagrisso (osimertinib) Section 4_ Utilisation and cost model.xlsx' spreadsheet of the submission.

The redacted table shows that at year 5, the estimated net cost to the PBS would be $20 - $30 million per year.

6.61 The ESCs noted that the PSCR (p7) addressed the issues regarding the mean treatment duration assumptions in the economic model and the financial estimates (see paragraph 6.34), and presented revised financial estimates accounting for a revised treatment duration of [redacted] months.

6.62 The displacement of chemotherapy to third-line was assumed to replace current third-line use of nivolumab. The proportion of patients who would currently receive third-line nivolumab may be an overestimate due to the requirement in the listing recently recommended by the PBAC for a PS of 0-1.

6.63 As the PBS items that would be reduced with the listing of osimertinib are administered by intravenous infusion, savings to the MBS were claimed in the basis of a reduction in these services. This was considered to be reasonable.

6.64 The submission did not consider the potential for osimertinib use in patients who are unable to tolerate a rebiopsy, but are tested privately using a plasma sample. This use would be allowed within the proposed PBS restriction, as it did not specify sample type to be tested.

6.65 The PSCR (p7) presented revised financial estimates, which were not independently verified, accounting for (i) potential for osimertinib use in patients who would be clinically ineligible for a tumour rebiopsy, but would be tested privately using a plasma sample; (ii) inclusion of patients with early stage NSCLC with a 20% rate of recurrence; and (iii) a mean treatment duration of [redacted] months.

6.66 These revised estimates are presented in the table below.

Table 17: Revised financial estimates presented in the PSCR

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Number of treated patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of T790M tests	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET cost to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET cost to MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
NET cost to Government	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net cost to the PBS would be $30 - $60 million per year.

6.67 The PSCR (p7) further stated that these estimates were likely to be inflated, as (i) the impact of a small number of private tests using plasma samples which flow on to PBS access would be much lower than that presented if an MBS item for tumour testing was recommended; and (ii) the number of patients receiving first-line EGFR TKI agents assumed in these estimates was more than that from a recent DUSC evaluation.

6.68 The ESCs considered that assuming a mean treatment duration of [redacted] months was appropriate (as discussed in paragraph 6.33), especially as the dose reductions to the

40 mg would have no impact on the cost of osimertinib treatment as the 40 mg pack was priced identically to the 80 mg pack.

6.69 Testing could occur in the first-line setting for de novo *T790M* mutations in order to exclude patients from treatment with first-line TKIs[5]. The approved TGA indication does not specifically exclude use of osimertinib in the first-line setting. Such use of osimertinib was not explored in the submission. There is an ongoing trial (FLAURA; NCT02296125) examining the comparative effectiveness of osimertinib relative to erlotinib or gefitinib in the first-line advanced NSCLC setting. The requested PBS restriction specifies use only after failure to first-line TKIs. The ESCs advised that there would be a significant risk of leakage to first-line therapy, especially given that a trial of osimertinib is underway in this setting (FLAURA) (see paragraph 3.2).

6.70 The costs associated with *T790M* testing and osimertinib use may have been underestimated, as:

- only patients with Stage IIIB/IV disease at diagnosis were considered;
- the number of packs per patient may be an underestimate; and
- there would be potential for broader use, both within and outside of the proposed restrictions.

Therefore, the net cost to the Australian Government health budget may be underestimated.

Financial management – risk sharing arrangements

6.71 The submission noted that the sponsor would be willing to enter into a risk sharing arrangement regarding the uncertainty in the expected eligible patient population for osimertinib – where there are higher than expected number of eligible patients receiving osimertinib therapy, [redacted]. The submission did not provide specific information regarding these annual patient numbers. The ESCs considered that a risk sharing arrangement was warranted to address the uncertainties in the estimated patient numbers, and to mitigate the risk of leakage to first-line therapy (see paragraphs 3.2 and 6.59).

6.72 The pre-PBAC response (p6) proposed more details of a risk sharing arrangement to mitigate the uncertainties in the financial estimates, [redacted].

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

7 PBAC outcome

7.1 The PBAC decided not to recommend osimertinib for the treatment of *EGFR T790M* mutation positive non-small cell lung cancer. Although accepting that osimertinib is more effective than standard chemotherapy, the PBAC advised that the magnitude of incremental overall survival benefit was difficult to determine from the evidence presented in the submission, and this was an important driver of the economic

[5] The T790M mutation is assumed to confer resistance to first- and second-generation EGFR TKIs by steric hindrance and increasing the binding affinity of *EGFR* for adenosine triphosphate (ATP)

evaluation. Additionally, the PBAC had concerns with other aspects of the economic model, which resulted in a high and overly optimistic estimated incremental cost effectiveness ratio at the price requested by the submission.

7.2 The PBAC noted that the codependent test for *EGFR T790M* mutations would be considered by the Medical Services Advisory Committee (MSAC) in late November 2017.

7.3 The PBAC sought further advice from MSAC on whether plasma or rebiopsy of tumour tissue would be the most appropriate source of biological material to inform *EGFR T790M* mutation status in this context. The PBAC also foreshadowed its intention to restrict any initial treatment criteria for osimertinib to an Authority Required (in writing). The PBAC advised that the restriction requested by the sponsor, with proposed changes by the Secretariat, was otherwise appropriate.

7.4 The PBAC considered that the submission's proposed place in therapy was appropriate, noting that there was unmet clinical need as patients with this condition develop acquired resistance to first-line EGFR TKI therapy, as confirmed during the sponsor hearing.

7.5 The PBAC considered that platinum-based doublet chemotherapy was the appropriate comparator.

7.6 The PBAC noted that the submission 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. The PBAC noted that the submission's claim of superior effectiveness was based on a gain in median PFS of 5.7 months in favour of osimertinib (10.1 months versus 4.4 months; HR 0.30 [0.23, 0.41]), at a median follow-up of [redacted] months.

7.7 The PBAC considered that OS data from AURA3 was immature, [redacted]. Further, the PBAC considered that the OS results were contaminated as [redacted]% of patients randomised to the chemotherapy arm had switched to osimertinib upon progression at the time of the interim analysis.

7.8 The PBAC noted that, instead of adjusting for treatment switching in the AURA3 trial, the submission 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 noted the arguments in the pre-PBAC response (p2-3) stating that a naïve indirect comparison was more appropriate than a statistical adjustment for treatment switching, but advised that the less scientifically rigorous naive indirect comparison presented in the submission introduced more rather than less uncertainty. By comparison, the AURA3 trial represented a more scientifically rigorous source of evidence and therefore more mature data from this trial based on an ITT analysis, or possibly based on a well-justified adjustment for treatment switching, would have been preferred.

7.9 The PBAC's main concern with the naïve indirect comparison was the high risk of bias due to the inherent limitations of indirect comparisons and the lack of a common reference arm. The PBAC also noted that *T790M* status in the chemotherapy arm

from the IMPRESS trial was determined in an exploratory manner via plasma-based testing. Although the PSCR (p1) contended that a comparison of the chemotherapy arm results from the IMPRESS and AURA3 trials suggested a similarity in efficacy outcomes, and hence did not support the suggestion of a differing prognostic effect for patients with a plasma T790M mutation in the IMPRESS trial, the PBAC considered that the selection bias arising from relying on plasma-based testing was likely to favour osimertinib.

7.10 Additionally, the PBAC considered that the OS data was immature in all of the evidence presented in the submission to support its claim of osimertinib's superior OS effect over chemotherapy, noting that [redacted]% and [redacted]% of patients treated with osimertinib in the AURA3 and AURA Pooled studies, had died at [redacted] and [redacted] months, respectively. The longer follow-up results from the AURA Pooled studies subsequently presented at a conference and referred to in the PSCR and pre-PBAC response did not provide a more convincing basis to accept any estimate of incremental OS benefit with osimertinib.

7.11 Overall, the PBAC advised that, while the submission's claim of superiority compared with platinum-based doublet chemotherapy was reasonable in terms of response rates, PFS, and safety based on the results of the AURA3 trial, the magnitude of incremental benefit in OS, if any, over chemotherapy, was inconclusive due to the immaturity of the OS data from AURA3 and the high rate of switching from chemotherapy to osimertinib. For the reasons given above, the PBAC advised that the results of the naïve indirect comparison of single-arm studies (AURA Pooled and IMPRESS) were not reliable enough to compensate for the limitations of the AURA3 trial.

7.12 The PBAC noted that the submission 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 considered that the submission's choice of a base case 10-year time horizon was unrealistically long and therefore implausible overly optimistic, as the committee:

- recalled that it had previously accepted a 5-year time horizon for first-line treatments of NSCLC (erlotinib and afatinib PSDs, July 2013 PBAC meeting);
- noted that the proposed place in therapy for osimertinib is in the second-line setting, and therefore at a later stage in disease than erlotinib and afatinib;
- noted ESC's concerns regarding the time horizon (see paragraph 6.45), particularly noting that patients in the chemotherapy arm of the model had died by 5 years, demonstrating consistency with current expectations of prognosis for this population;
- noted that, at the sponsor hearing, the clinician stated that acquired resistance would develop to osimertinib in this condition; and
- noted that changing the time horizon to 5 years resulted in an increase in the ICER from a base case of $75,000/QALY - $105,000/QALY to $75,000/QALY - $105,000/QALY.

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.

7.14 Additionally, the PBAC considered that another issue with the economic model was 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.

7.15 The PBAC considered that the cost of osimertinib used in the economic model was an underestimate, as it was based on the observed mean duration of treatment on osimertinib in the AURA3 study. The PBAC noted that this was a truncated mean, as [redacted]% of patients were still on osimertinib treatment at the latest data cut-off.

- The PBAC noted that, on applying the cost of osimertinib on a per cycle basis until disease progression consistent with the requested continuation criteria, the ICER increased from $75,000/QALY - $105,000/QALY to $75,000/QALY - $105,000/QALY (reflecting the extrapolated mean PFS for osimertinib of [redacted] months);
- Arguing that this approach did not account for dose interruptions or reductions due to tolerability, the PSCR (p3) and pre-PBAC response (p5) stated that, at the time of the submission, the "actual" mean treatment duration was [redacted] months versus a "total" median treatment duration of [redacted] months, resulting in a relativity of [redacted]. Applying this dose relativity resulted in an ICER of $75,000/QALY - $105,000/QALY (not independently verified).
- The PBAC considered that, while the basis of this argument was not unreasonable, the progression-free health state modelling up to a progression event was based on the AURA3 trial, whereas the PSCR and the pre-PBAC response relied on the AURA Pooled studies to calculate its ratio of "actual" to "total" duration above.
- Using these median values from the AURA3 trial[6] instead resulted in a ratio of [redacted]. Further, the PBAC noted that the mean relative dose intensity (RDI) in the AURA3 trial was reported to be [redacted].

As such, the PBAC considered that substituting data from another clinical source for this variable rather than from the AURA3 trial reduced the internal validity of the estimate for the model, and therefore advised that the cost-effectiveness of osimertinib was likely to be much closer to the $75,000/QALY - $105,000/QALY estimate, rather than the submission's base case of $75,000/QALY - $105,000/QALY, or the $75,000/QALY - $105,000/QALY ICER from the PSCR.

[6] AURA3 Addendum to Clinical Study Report, page 54 and Table 13

7.16 The PBAC noted that the PSCR (p7) presented revised financial estimates, which were not independently verified, accounting for (i) potential for osimertinib use in patients who would be clinically ineligible for a tumour rebiopsy, but would be tested privately on plasma samples; (ii) inclusion of patients with early stage NSCLC with a 20% rate of recurrence; and (iii) a mean treatment duration of [redacted] months. However, the PBAC considered that uncertainty 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.

7.17 The PBAC noted that the sponsor had indicated a willingness to enter into a risk sharing arrangement to address the uncertainty about greater than expected numbers of eligible patients receiving osimertinib therapy each year arising from leakage into the first-line setting.

7.18 The PBAC noted that the pre-PBAC response (p3,6) proposed an MES to address the uncertainties regarding OS, and/or a risk sharing arrangement to mitigate the uncertainties in the financial estimates. The PBAC advised that the fundamental flaws in the economic model would need to be amended via a resubmission, before this option could be appropriately considered by the Committee. In addition, the PBAC foreshadowed that the base case of such an MES would need to be based on the ITT analysis of AURA3 so that the uncertainty created by the post-progression switching to osimertinib in the comparator arm does not become an unpredictable source of dispute in the revised economic evaluation reflecting the end of the MES. The PBAC foreshadowed that a single-arm retrospective analysis of first-line TKI use from an Australian lung cancer registry would not reduce uncertainty in the estimate of incremental OS and could not be used as the basis for an MES.

7.19 The PBAC noted that this submission was eligible for an independent review.

Outcome:

Rejected

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.