6.07 OSIMERTINIB, Tablet 40 mg, 80 mg, Tagrisso®, AstraZeneca Pty Ltd.

1 Purpose of Application

1.1 The submission requested a Section 85, Authority Required listing for osimertinib as the first-line treatment of locally advanced or metastatic (Stage IIIB or IV), epidermal growth factor receptor (EGFR) mutation positive (M+), non-small cell lung cancer (NSCLC). This was the first submission for osimertinib for this indication.

1.2 The key components of the clinical issue addressed by the submission are presented below.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Treatment-naïve, locally advanced or metastatic EGFR M+ NSCLC patients
Intervention	Osimertinib 80mg tablet once daily until disease progression or unacceptable toxicity
Comparator	Erlotinib 150mg tablet once daily until disease progression or unacceptable toxicity; and Gefitinib 250mg tablet once daily until disease progression or unacceptable toxicity
Outcomes	PFS, OS, ORR, DCR, QoL and AEs
Clinical claim	In patients with locally advanced or metastatic EGFR M+ NSCLC, osimertinib is superior to erlotinib and gefitinib in terms of efficacy, QoL and safety.

AE = adverse event; DCR = disease control rate; EGFR M+ = epidermal growth factor receptor mutation positive; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; QoL = quality of life
Source: Adapted from Table 1.1-1, p17 of the submission.

2 Requested listing

2.1 The submission presented the proposed listing for first-line listing of osimertinib, which was to be separate to the current listing for second-line osimertinib. The Pre-Sub-Committee Response (PSCR) considered a line agnostic listing for osimertinib would also be reasonable. Suggestions and additions proposed by the Secretariat regarding a line-agnostic listing are added in italics.

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Osimertinib					Tagrisso® AstraZeneca Pty Ltd
Tablets 80mg	1	30	5	$7,957.88 published price [redacted] effective price	
Tablets 40mg	1	30	5	$7,957.88 published price [redacted] effective price	

Category / Program	*Section 85 – General Schedule*
Prescriber type	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *Midwives*
Condition	*Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)*

Treatment phase	*Initial treatment*
Restriction	☐ *Restricted benefit* ☐ *Authority Required – In Writing* ☒ *Authority Required – Telephone/Electronic/Emergency* ☐ *Streamlined*
Clinical criteria	*The treatment must be the sole PBS-subsidised therapy for this condition,* *AND* *Patient must have a WHO performance status of 2 or less,* *AND* *Patient must not have previously received PBS-subsidised treatment with this drug for this condition.* *AND* *Patient must not have received previous PBS-subsidised treatment with another epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)* *OR* *Patient must have developed intolerance to another EGFR TKI of a severity necessitating permanent treatment withdrawal* *OR* *Patient must have evidence of EGFR T790M mutation in tumour material at the point of progression on or after first line EGFR TKI treatment.*
Population criteria	*Patient must have evidence of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors in tumour material.*
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.*

Category / Program	*Section 85 – General Schedule*
Prescriber type	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *Midwives*
Condition	*Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)*
Treatment phase	*Continuing treatment*
Restriction	☐ *Restricted benefit* ☐ *Authority Required – In Writing* ☐ *Authority Required – Telephone/Electronic/Emergency* ☒ *Streamlined*
Clinical criteria	*The treatment must be the sole PBS-subsidised therapy for this condition,* *AND* *Patient must have previously received PBS-subsidised treatment with this drug for this condition,* *AND* *Patient must not have developed disease progression while receiving 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.*

Category / Program	*Section 85 – General Schedule*
Prescriber type	☐ *Dental* ☒ *Medical Practitioners* ☐ *Nurse practitioners* ☐ *Optometrists* ☐ *Midwives*
Condition	*Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)*
Treatment phase	*Grandfather treatment*
Restriction	☐ *Restricted benefit* ☐ *Authority Required – In Writing* ☒ *Authority Required – Telephone/Electronic/Emergency* ☐ *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 the sole PBS-subsidised therapy for this condition,* *AND* *Patient must have had a WHO performance status of 2 or less prior to initiating non-PBS-subsidised treatment,* *AND* *Patient must not have developed disease progression while receiving non-PBS-subsidised treatment with this drug for this condition.*
Population criteria	*Patient must have had evidence of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors in tumour material prior to initiating non-PBS subsidised treatment*
Prescribing Instructions	*A patient may qualify for PBS-subsidised treatment under this restriction once only.* *For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria.*
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.*

Note: The 80 mg strength is for both initial treatment and continuing treatment; whilst the 40 mg strength is only for continuing treatment.

2.2 Osimertinib is currently listed on the PBS for treatment of locally advanced or metastatic NSCLC in patients who have progressed on or after EGFR-TKI therapy and whose tumours are tested positive for a T790M mutation (PBS item numbers 11620N and 11622Q). The Pre-Sub-Committee Response (PSCR) stated that plasma samples of patients treated with osimertinib in the FLAURA trial did not detect T790M mutations on progression. The ESC considered that there is no clinical rationale for continuing or retreating with osimertinib after progression whether tumours are T790M M+ or not. Therefore, the ESC considered that the current PBS restriction for osimertinib did not require any additional restrictions to preclude such use and a second biopsy to test for T790M mutation would not be likely to occur. However, the ESC noted that if a criterion is to be included, it should align with the restrictions for erlotinib and gefitinib. Alternatively, the PSCR also stated that a line agnostic restriction which combined first and second-line osimertinib treatment would be reasonable. The PBAC considered a line agnostic restriction would be appropriate.

2.3 The submission proposed a minor amendment to the current MBS Item 73337, which is a tumour tissue test to determine EGFR status for access to erlotinib, gefitinib and afatinib under the PBS. This amendment requested the addition of osimertinib to the list of TKI agents for which Item 73337 can be used to determine PBS eligibility. The submission did not expect this revision to have an impact on the number of tests performed in clinical practice or on the cost to the MBS because an EGFR test is required for other TKIs currently listed on the PBS. The PBAC noted that this change would be reasonable if a line agnostic restriction was implemented.

2.4 The submission proposed a Special Pricing Arrangement (SPA) for osimertinib with the effective price representing a [redacted]% rebate on the published dispensed price for maximum quantity (DPMQ). The requested effective DPMQs are in line with the

current effective DPMQs for second-line osimertinib, while the published DPMQs for second-line osimertinib are slightly higher, at $7,961.04 for both strengths.

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

3 Background

Registration status

3.1 Osimertinib was registered by the TGA in August 2016 for the following indications:

- For the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have activating EGFR mutations; and
- For treatment of patients with locally advanced or metastatic EGFR T790M M+ NSCLC.

Previous PBAC consideration

3.2 In November 2018, the PBAC recommended osimertinib for listing on the PBS for the treatment of patients with locally advanced or metastatic NSCLC in patients who have progressed on or after prior EGFR-TKI therapy and whose tumours are tested positive for T790M (referred to as second-line treatment). Osimertinib was listed on the PBS on 1 February 2019.

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

4 Population and disease

4.1 Lung cancer is the fifth most commonly diagnosed cancer in Australia and the most common cause of cancer-related death, accounting for 18.9% of cancer-related deaths. Due to early-stage lung cancer being largely insidious, more than 50% of patients were diagnosed at an advanced or inoperable stage[1].

4.2 In Australia, 15% to 26% of NSCLC patients have tumours harbouring an activating mutation in the EGFR gene, which confers sensitivity to EGFR-TKIs[2]. Two main classes of activating mutations that are sensitive to TKIs are exon 19 deletions (Ex19del) and L858R point mutation in exon 21.

[1] AIHW. Cancer incidence projections Australia, 2011 to 2020. Cat. no. CAN 62. 2012. Available from: https://www.aihw.gov.au/reports/cancer/cancer-incidence-projections-australia-2011-to-20/contents/table-of-contents; AIHW, Cancer Australia. Lung cancer in Australia: an overview. Cat. no. CAN 58. 2011. Available from: https://www.aihw.gov.au/reports/cancer/lung-cancer-in-australia-overview/contents/table-of-contents.

[2] IPSOS. Overview of the NSCLC cancer treatment landscape - 2018 Q2 IPSOS Global Oncology Monitor in Australia. 2018; Peters MJ, Bowden JJ, *et al*. Outcomes of an Australian testing programme for epidermal growth factor receptor mutations in non-small cell lung cancer. *Intern Med J*. 2014;44(6):575-80.

4.3 The population proposed for treatment with osimertinib is treatment-naïve patients with locally advanced (Stage IIIB) or metastatic (Stage IV) EGFR M+ NSCLC. The ESC considered this to be appropriate.

4.4 The ESC noted that if osimertinib is listed for first line treatment, it is anticipated that all patients would be treated with osimertinib in preference over early generation TKIs, resulting in a substantial reduction in use of erlotinib and gefitinib.

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

5 Comparator

5.1 The submission nominated erlotinib and gefitinib as the main comparators. The main argument provided in support of this nomination was that erlotinib and gefitinib are the most commonly used first-line therapy for EGFR M+ NSCLC.

5.2 As noted earlier, patients who have progressed on or after erlotinib or gefitinib and who have evidence of EGFR T790M mutation in tumour material at the point of progression are eligible for PBS subsidised osimertinib as a second-line treatment. The submission stated that acquired T790M resistance mutation occurs in approximately 60% of patients who undergo biopsy on disease progression. The availability of first-line osimertinib on the PBS would substitute for both the first-line early-generation TKIs, e.g. erlotinib and gefitinib, and second-line osimertinib if patients developed T790M mutation. Therefore, the ESC considered that sequential TKI use of erlotinib or gefitinib followed by second-line osimertinib for eligible patients would have been the more appropriate comparator for the group of patients who develop the T790M mutation.

5.3 For those patients who do not have evidence of EGFR T790M mutation at the point of progression following treatment with first-line erlotinib or gefitinib, platinum-based doublet chemotherapy would be the standard of treatment, which is the same treatment as following the proposed first-line osimertinib treatment. Therefore, the ESC considered that, for this group of patients, the submission's nominated comparators of erlotinib and gefitinib were appropriate.

5.4 The PSCR stated that, "the target population for first-line osimertinib is patients with EGFR M+ NSCLC who are currently treated with erlotinib or gefitinib. Consequently, both erlotinib and gefitinib are the medicines that will be replaced in this target population and are therefore the main comparators. As for any medicine proposed for PBS listing, there are downstream changes in the treatment algorithm. Those changes occur in a different target population and should therefore not form part of the comparator. It is important to note, however, that the impact of downstream changes in the treatment algorithm have been considered in the submission." The ESC considered that for patients who develop a T790M mutation at the point of progression, first-line treatment with osimertinib will replace not just first-line treatment with erlotinib or gefitinib but also second-line osimertinib. Nevertheless,

the ESC agreed with the PSCR that this would not be an issue if the submission's economic model incorporated the likely impact of downstream changes in the treatment algorithm. In this regard, the ESC considered the comparator arm of the model was not reflective of current standard care (see paragraphs 6.32-6.33).

5.5 Afatinib is a second-generation TKI which was listed on the PBS in May 2018. However, the use of afatinib was reported to be negligible[3]. Expert opinion advised that this is due to the unfavourable safety profile of afatinib and that the market share of afatinib is unlikely to increase. The submission further argued that the comparison of osimertinib versus erlotinib and gefitinib is applicable to afatinib: given that: i) the PBAC previously considered that erlotinib, gefitinib and afatinib are clinically non-inferior to each other (Erlotinib PSD, July 2013 PBAC meeting); and ii) afatinib and gefitinib were listed on the PBS on a cost-minimisation basis with erlotinib.

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. Based on their experience with prescribing osimertinib to patients, the clinician considered osimertinib to be more effective at improving PFS and better tolerated than current first-line TKI treatments. The clinician presented a case study and noted that first-line osimertinib was associated with improved activity in the central nervous system and that prevention of cranial and leptomeningeal disease which is an important clinical outcome. In terms of toxicity, the clinician noted that osimertinib had lower levels of skin toxicity and diarrhoea when compared to early generation TKIs. The clinician noted that there is no evidence for biomarkers and further research is required to determine the impact of chemotherapy in addition to TKIs. The sponsor clarified the RSA proposal presented in the pre-PBAC response (further details provided in Financial Management section). The sponsor also noted that updated data regarding the OS benefits of osimertinib from the FLAURA trial would be available in the near future for PBAC to assess. The PBAC considered that the hearing was informative as it provided a clinical perspective on osimertinib as well as further clarity around the RSA.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (10) and organisations (2) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with osimertinib including the ability to go to work, less impact on ability to perform physical activities and more tolerable side effects

[3] IPSOS. Overview of the NSCLC cancer treatment landscape - 2018 Q2 IPSOS Global Oncology Monitor in Australia. 2018.

including less skin rashes and mouth toxicity, no loss of hair or appetite, compared with erlotinib.

6.3 The PBAC noted the advice received from Lung Foundation Australia highlighting the likely use of osimertinib in clinical practice. Based on the FLAURA trial evidence and a case study, the advice noted that for patients with Stage IV EGFR NSCLC, osimertinib increases PFS, significantly delaying onset and improving quality of life and general wellbeing, and potentially prevents the onset of brain metastases. Lung Foundation Australia considered that osimertinib is superior to TKIs currently used as first-line treatment and patients should not have to wait for their cancer to progress before they can access this treatment. The organisation expects that first-line treatment with osimertinib would be offered as routine standard of care, in preference to early-generation TKIs, for this patient population who currently have poor survivability and limited effective treatment options available to them. The PBAC noted that this advice was supportive of the evidence provided in the submission.

6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the osimertinib submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of improved PFS based on the FLAURA trial. The PBAC noted that the MOGA presented a 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)[4], based on a comparison with erlotinib and gefitinib. MOGA noted that the ESMO-MCBS score will increase to a 5 if mature data demonstrates an improvement in OS.

Clinical trials

6.5 The submission was based on one head-to-head trial (FLAURA) comparing osimertinib with erlotinib/gefitinib in Stage IIIB or IV NSCLC patients who had not received any prior treatment for their advanced/metastatic disease and whose tumour harboured Ex19del or L858R, either alone or in combination with other EGFR mutations (N=556). The ESC considered the FLAURA trial was applicable to the Australian population.

6.6 Details of the trial presented in the submission are provided in the table below.

Table 2: Trial and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
FLAURA	A Phase III, double-blind, randomised study to assess the efficacy and safety of AZ9291 versus a standard of care epidermal growth factor receptor-tyrosine kinase inhibitor as first-line treatment in patients with epidermal growth factor receptor mutation-positive, locally-advanced or metastatic non-small-cell lung cancer (FLAURA).	September 2017
	Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in Untreated EGFR-Mutated Advanced Non-Small-Cell Lung Cancer.	*N Engl J Med* 2018; 378(2): 113-25.
	Reungwetwattana T, Nakagawa K, Cho BC, et al. CNS response to osimertinib versus standard epidermal growth factor receptor tyrosine	*J Clin Oncol* 2018; 36(33): 3290-3297

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

Trial ID	Protocol title/ Publication title	Publication citation
	kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer.	
	Leighl N, Karaseva N, Nakagawa K, et al. Patient-reported outcomes from FLAURA: osimertinib versus standard of care epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) in patients with EGFR-mutated advanced non-small cell lung cancer (abstract)	8th European Lung Cancer Conference. April 2018

Source: Table 2.2-1, p38 of the submission.

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

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
osimertinib vs. erlotinib/gefitinib						
FLAURA	556	R, DB 18 months*	Low	Treatment-naïve locally advanced (Stage IIIB) or metastatic (Stage IV) EGFR M+ NSCLC	PFS, OS	Used

DB = double blind; EGFR = epidermal growth factor receptor; M+ = mutation positive; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; R = randomised.
* Median duration of follow-up for OS data was 18.6 months in the osimertinib arm and 17.4 months in the comparator arm (sourced from Table 21, p131 of the clinical study report).
Source: Generated during the evaluation based on Sections 2.3 and 2.4, pp39-60 of the submission.

Comparative effectiveness

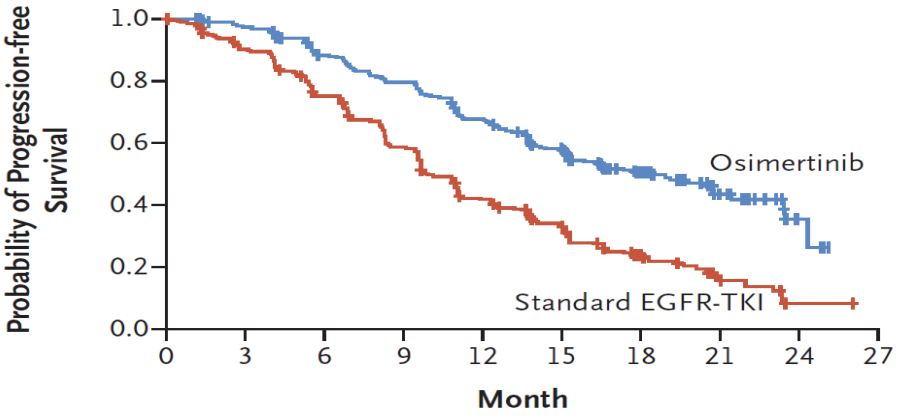
6.8 Results of PFS, based on investigator assessment, at the data cut-off 1 (June 2017) for the primary analysis are presented below.

Table 4: Results of progression-free survival in FLAURA (investigator-assessed, June 2017 data cut-off)

	Osimertinib N = 279	Erlotinib/gefitinib N = 277	Treatment effect (95% CI)	p-value
Events, n (%)	136 (48.7)	206 (74.4)		
Median PFS, months (95% CI)	18.9 (15.2, 21.4)	10.2 (9.6, 11.1)	HR: 0.46 (0.37, 0.57)	< 0.0001
% of patients progression-free by time point (95% CI)			Risk difference:	
6 months	88.4 (83.9, 91.7)	75.2 (69.5, 79.9)	13.2	
12 months	68.2 (62.3, 73.5)	42.3 (36.3, 48.2)	25.9	
18 months	50.9 (44.5, 57.0)	24.4 (19.2, 30.0)	26.5	
24 months	35.8 (25.6, 46.2)	8.4 (3.5, 15.9)	27.4	

CI = confidence interval; PFS = progression-free survival; HR = hazard ratio.
Source: Table 2.5-2, p62 of the submission

Figure 1: Kaplan-Meier curves for progression-free survival in FLAURA (investigator assessed, June 2017 data cut-off)



No. at Risk										
Osimertinib	279	262	233	210	178	139	71	26	4	0
Standard EGFR-TKI	277	239	197	152	107	78	37	10	2	0

EGFR-TKI = epidermal growth factor receptor- tyrosine kinase inhibitor
Source: Figure 2.5-1, p62 of the submission

6.9 Based on the Kaplan Meier analysis, the estimated proportion of patients alive and progression-free (investigator-assessed, Response Evaluation Criteria In Solid Tumours (RECIST)-defined) was 50.9% in the osimertinib arm and 24.4% in the erlotinib/gefitinib arm at 18 months. The median PFS was 18.9 months for osimertinib, which was 8.7 months longer than the median PFS in the comparator arm (10.2 months). First-line osimertinib was associated with a statistically significant reduction in the risk of disease progression or death compared to erlotinib and gefitinib, with a hazard ratio (HR) of 0.46 (95% confidence interval (CI): 0.37 to 0.57; P<0.001). The difference is likely to be clinically meaningful. Similar results were reported for PFS as determined by blinded independent central review (BICR) of the imaging (median PFS: 17.7 months vs. 9.7 months; HR: 0.46 (95% CI: 0.37, 0.57)).

6.10 The duration of follow-up was around 27 months in the FLAURA trial at the June 2017 data cut-off. By this time, 25% of the subjects had died. Results of the interim OS analysis at the June 2017 data cut-off are summarised below.

Table 5: Results of overall survival in FLAURA (interim analysis, June 2017 data cut-off)

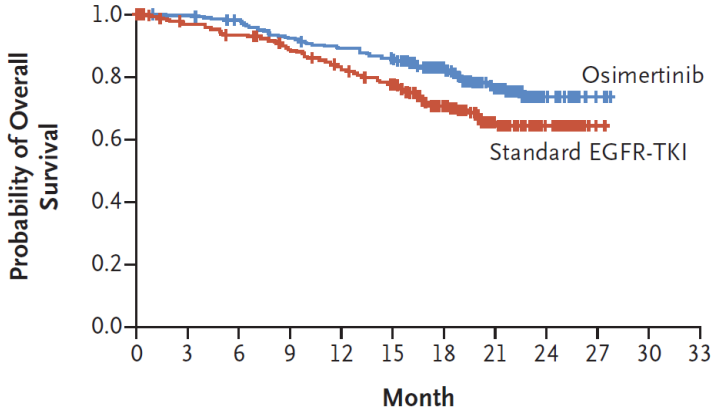
	Osimertinib N = 279	Erlotinib/gefitinib N = 277	Treatment effect (99.85% CI)[a]	p-value
Death, n (%)	58 (20.8)	83 (30.0)		
Median, months (95% CI)	NC (NC, NC)	NC (NC, NC)	HR: 0.63 (0.37, 1.08)	0.0068[a]
% survival by time point (95% CI)			Risk difference:	
6 months	98.2 (95.7, 99.2)	93.4 (89.7, 95.8)	4.8	
12 months	89.1 (84.7, 92.2)	82.5 (77.4, 86.5)	6.6	
18 months	82.8 (77.7, 86.8)	70.9 (64.8, 76.1)	11.9	
24 months	73.7 (66.4, 79.6)	64.7 (57.7, 70.9)	9.0	

CI = confidence interval; NC = not calculable; HR = hazard ratio.

[a] The adjusted CI was computed at the 2-sided 99.85% level, considering a 2-sided significance level of 0.0015 for the overall survival interim analysis, based on the O'Brien and Fleming spending function, assuming 318 deaths for the final overall survival analysis. The unadjusted 95% CI resulted in a HR of 0.63 (95% CI: 0.45, 0.88; p=0.068).

Source: Table 2.5-5, p66 of the submission

Figure 2: Kaplan-Meier curve for overall survival in FLAURA (interim analysis, June 2017 data cut-off)



No. at Risk

Osimertinib	279	276	269	253	243	232	154	87	29	4	0	0
Standard EGFR-TKI	277	263	252	237	218	200	126	64	24	1	0	0

Source: Figure 2.5-3, p67 of the submission

6.11 Median OS was not reached in either treatment group. A total of 141 patients died at the June 2017 data cut-off: 58 (20.8%) patients in the osimertinib arm and 83 (30.0%) patients in the comparator arm. The unadjusted results of the interim OS analysis showed a HR of 0.63 (95% CI: 0.45, 0.88; p=0.068). This extent of improvement, however, did not reach the formal statistical significance for the interim analysis (p<0.0015, determined by the O'Brien-Fleming approach for an interim analysis). Although the HR for OS appeared clinically relevant, the ESC considered the results should be interpreted with caution due to the immaturity of the OS data. The relative treatment effect may vary as more mature data become available. The magnitude of the survival benefits associated with osimertinib relative to erlotinib/gefitinib as first-line therapy for EGFR M+ NSCLC cannot be reliably estimated. [redacted]

[redacted] The sponsor expects the updated data to be available late 2019.

6.12 In addition, the use of second-line osimertinib in patients who discontinued randomised erlotinib/gefitinib therapy in FLAURA (29.1% of patients) may be lower than what would occur in clinical practice. The evaluation noted the second-line osimertinib PBAC submission assumed that around 49% of patients who progress following first-line treatment with earlier-generation EGFR TKIs would be treated with second-line osimertinib (based on 82% of progressed patients being eligible for biopsy, 60% prevalence of T790 M+ among these patients and 100% uptake). Accordingly, the OS benefit of first-line osimertinib compared with first-line erlotinib/gefitinib may have been overestimated in FLAURA compared with in clinical practice, and thus biased the result favouring first-line osimertinib.

- The PSCR argued that the commentary's calculation did not account for the patients who died or those who withdrew/terminated from the FLAURA clinical trial. The PSCR stated the proportion of patients who received subsequent treatment with osimertinib should be calculated by dividing the total number of patients who received any post-treatment anti-cancer therapy (129 patients) resulting in 48.1% of patients receiving subsequent treatment with osimertinib (Table 6). The pre-PBAC response further highlighted that this proportion is expected to increase as more patients experience disease progression, and have an opportunity to commence treatment with other subsequent therapies. Thus, the proportion of patients who receive subsequent osimertinib in the comparator arm is likely to increase from 48.1% to a proportion that will more closely reflect the prevalence of the T790M mutation post-progression (approximately 60%).
- The ESC acknowledged that 48.1% of erlotinib/gefitinib patients who received any post-treatment anti-cancer therapy received treatment with osimertinib. However, it considered that the proportion of patients receiving any subsequent therapies in the FLAURA trial (60% (129/213)) is an underestimate compared with clinical practice and reflected the immaturity of the trial data, in which around a quarter of patients in the erlotinib/gefitinib arm are still receiving their randomised treatment. Accordingly, the ESC considered the potential underuse of second-line osimertinib in patients who discontinued randomised erlotinib/gefitinib therapy in FLAURA compared with clinical practice remained a concern.

Table 6: First and second therapy regimens following randomised treatment in Trial FLAURA (June 2017 data cut-off)

	Osimertinib, n (%)[a] (N=279)	Erlotinib/gefitinib, n (%)[a] (N=277)
Discontinued randomised study treatment	138 (49.5)	213 (76.9)
Any post-treatment anti-cancer therapy	82 (29.4)	129 (46.6)
No anti-cancer therapy after randomised treatment	56 (20.1)	84 (30.3)
Ongoing randomised study treatment	141 (50.5)	64 (23.1)
Any post-treatment anticancer therapy[b]	**n = 82**	**n = 129**
EGFR-TKI	38 (46.3)	99 (76.7)
Osimertinib	–	62 (48.1)
Other TKIs	38 (46.3)	NR~
PD-1/PD-L1	6 (7.3)	4 (3.1)
Platinum-based chemotherapy	53 (64.6)	42 (32.6)
Non-platinum chemotherapy	55 (67.0)	46 (35.7)
Other targeted therapy	3 (3.7)	5 (3.9)
Anti-VEGF	10 (12.2)	14 (10.8)

EGFR-TKI = epidermal growth factor receptor- tyrosine kinase inhibitor; NR = not reported; PD-(L)1 = programmed cell death (ligand) 1; VEGF = vascular endothelial growth factor

Source: Pre-Sub-Committee Response (PSCR). Modified from Table 2.4.4 of the Commentary; FLAURA CSR, Table 12, p107

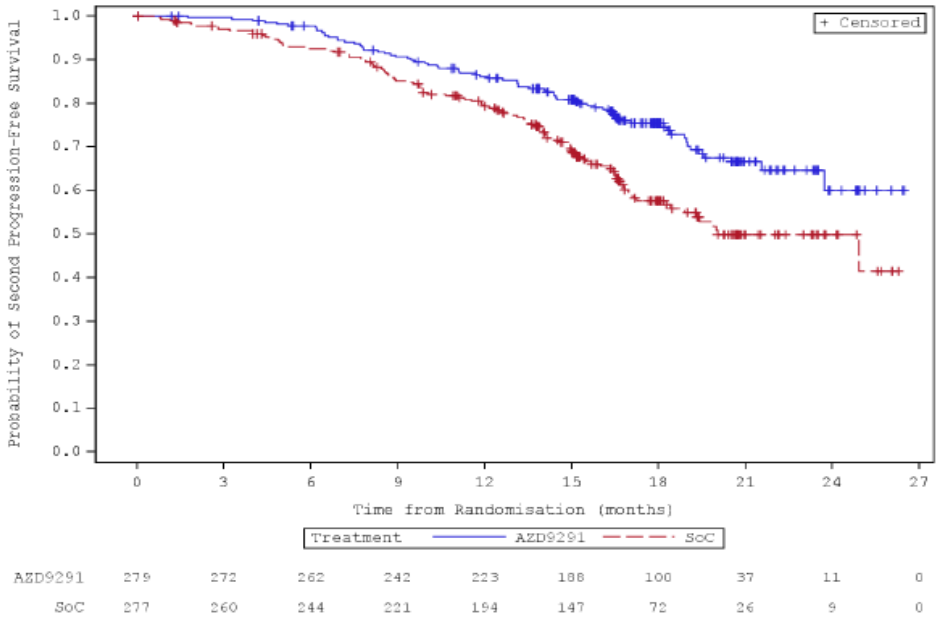
[a] The number of patients is shown with percentages calculated as the proportion of patients in the full analysis set

[b]The number of patients receiving post-treatment anticancer therapy is shown with percentages calculated based on the patients who received any post-treatment anti-cancer therapy

~As patients could receive both osimertinib and another TKI following randomised therapy, the numbers of patients treated with another TKI would be between 37 patients (number of patients receiving any TKI minus those receiving subsequent osimertinib) and 99 patients.

6.13 The PSCR claimed that the observed delay in time from randomisation to second progression (PFS2) (HR 0.58 [95% CI: 0.44, 0.78] p= 0.0004; Figure 3) in the FLAURA clinical trial demonstrated that the benefit of treatment with osimertinib continues beyond initial progression.

Figure 3: Kaplan-Meier plot of time to second progression on subsequent therapy



Source: Pre-Sub-Committee Report (PSCR), Figure 14 of CSR (p151)

6.14 The submission stated that two questionnaires (EORTC QLQ-C30 and EORTC QLQ-LC13) were used to assess changes in patient-reported disease-related symptoms and health-related quality of life (QoL), every 6 weeks for 18 months, then every 12 weeks until second PFS[5]. The proportion of patients who achieved a pre-specified change of 10 points in patient-reported key symptom scores at any time until randomised treatment discontinuation, mean changes in these symptom scores and in global health and functioning scores from baseline to randomised treatment discontinuation were reported in the submission. First-line osimertinib appeared to result in a greater improvement in patients' symptoms, functioning and global health status, compared with erlotinib/gefitinib, although the differences between the two treatment arms were not always statistically significant. None of these differences reached the clinically relevant cut-off of ≥10 points, defined in the FLAURA trial protocol.

Comparative harms

6.15 The results of adverse events (AEs) reported in FLAURA are summarised below.

Table 7: Summary of adverse events in FLAURA

AE category[a]	Osimertinib, n (%) N = 279	Erlotinib/gefitinib, n (%) N = 277	RD (95% CI)[b]	RR (95% CI)[b]
AEs of Grade ≥3	95 (34.1)	124 (44.8)	-10.7% (-18.8%, -2.6%)	0.76 (0.62, 0.94)
AEs of Grade ≥3, possibly related to treatment[c]	49 (17.6)	78 (28.2)	-10.6% (-17.5%, -3.7%)	0.62 (0.45, 0.86)
Fatal AEs	6 (2.2)	10 (3.6)	-1.5% (-4.2%, 2.3%)	0.60 (0.22, 1.62)
Fatal AEs, possibly related to treatment[c]	0	1 (0.4)	-0.4% (-1.1%, 0.3%)	0
SAEs	60 (21.5)	70 (25.3)	-3.8% (-10.8%, 3.3%)	0.85 (0.63, 1.15)
SAEs, possibly related to treatment[c]	22 (7.9)	23 (8.3)	-0.4% (-5.0%, 4.1%)	0.95 (0.54, 1.66)
AEs leading to discontinuation of study treatment	37 (13.3)	49 (17.7)	-4.4% (-10.4%, 1.6%)	0.75 (0.51, 1.11)
AEs leading to discontinuation of study treatment, possibly related to treatment[c]	27 (9.7)	38 (13.7)	-4.0% (-9.4%, 1.3%)	0.71 (0.44, 1.12)

AE = adverse event; CI = confidence interval; RD = risk difference; RR = relative risk; SAE = serious adverse event

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each category.

[b] RR and RD were calculated during the evaluation, using the 'csi' command in Stata 14 software

[c] As assessed by the investigator. 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 cross-over treatment.

Source: Table 2.5-8, p72 of the submission

6.16 Almost all patients in both treatment arms experienced at least one AE. The occurrence of ≥ Grade 3 AEs (34.1% vs. 44.8%) and treatment-related ≥ Grade 3 AEs

[5] Second PFS: the earliest of the progression event subsequent to PFS (primary endpoint) or date of death after starting subsequent anti-cancer therapy.

(17.6% vs. 28.2%) was statistically lower in patients treated with osimertinib than in patients receiving erlotinib or gefitinib. Osimertinib was generally well-tolerated, with a numerically lower percentage of patients having AEs leading to drug discontinuation in the osimertinib arm than in the erlotinib/gefitinib group (13.3% vs. 17.7%).

6.17 Data on AEs of special interest were collected in FLAURA. The clinical study report (CSR) noted that interstitial lung disease (ILD) or ILD-like events were reported in 11 patients (3.9%) in the osimertinib arm compared with six patients (2.2%) in the erlotinib/gefitinib arm. QT prolongation was reported in 10.0% of patients who received osimertinib, compared to 4.0% of those who received erlotinib/gefitinib. There were eight (3.1%) patients in the osimertinib group and three (1.2%) patients in the comparator group who had left ventricular ejection fraction (LVEF) decreasing from baseline of ≥10 percentage points to an LVEF absolute value of <50%; and an LVEF decrease of ≥15 percentage points to an LVEF absolute value ≥50% was observed in 25 (9.7%) patients on osimertinib and 16 (6.3%) patients on erlotinib/gefitinib.

6.18 Overall, the pattern of AEs reported in both treatment arms of FLAURA was as expected for an advanced NSCLC patient population receiving an EGFR-TKI in the first-line setting. Safety findings in the osimertinib arm were broadly consistent with the known safety profile of osimertinib, including prolongation of QT interval, cardiac contractibility and ILD, with no new safety signal identified.

Benefits/harms

6.19 A summary of the comparative benefits and harms for osimertinib versus erlotinib/gefitinib as observed from FLAURA is presented in the table below.

Table 8: Summary of comparative benefits and harms for osimertinib versus erlotinib/gefitinib

Benefits (at data cut-off 1[a])				
Event	**Osimertinib**	**Erlotinib/gefitinib**	**Absolute Difference**	**HR (95% CI)**
PFS				
Progressed or died, n (%)	136/279 (48.7%)	206/277 (74.4%)		
Median PFS (95% CI), months	18.9 (15.2, 21.4)	10.2 (9.6, 11.1)		0.46 (0.37, 0.57) P<0.0001
% progression-free at 12 months (95% CI)	68.2% (62.3%, 73.5%)	42.3% (36.3%, 48.2%)	25.9%	
% progression-free at 18 months (95% CI)	50.9% (44.5%, 57.0%)	24.4% (19.2%, 30.0%)	26.5%	
Overall survival				
Deaths, n/N (%)	58/279 (20.8%)	83/277(30.0%)		
Median OS (95% CI) months	NC (NC, NC)	NC (NC, NC)		0.63 (0.37, 1.08) P=0.0068[b]
% Alive at 12 months (95% CI)	89.1% (84.7%, 92.2%)	82.5% (77.4%, 86.5%)	6.6%	
% Alive at 18 months (95% CI)	82.8% (77.7%, 86.8%)	70.9% (64.8%, 76.1%)	11.9%	

Harms						
AE Category	**Osimertinib n/N**	**Erlotinib/gefitinib n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Osimertinib	**Erlotinib/gefitinib**	

AE of Grade ≥3	95/279	124/277	0.76 (0.62, 0.94)	34.1	44.8	-10.7% (-18.8%, -2.6%)
Serious AEs	60/279	70/277	0.85 (0.63, 1.15)	21.5	25.3	-3.8% (-10.8%, 3.3%)
AEs leading to discontinuation of study drug	37/279	49/277	0.75 (0.51, 1.11)	13.3	17.7	-4.4% (-10.4%, 1.6%)

AE = adverse event; CI = confidence interval; HR = hazard ratio; NC = not calculable; OS = overall survival; PFS = progression-free survival; RD = risk difference; RR = relative risk.

[a] The maximum duration of follow-up was around 27 months at DOC1.

[b] The adjusted CI was computed at the 2-sided 99.85% level, considering a 2-sided significance level of 0.0015 for the overall survival interim analysis, based on the O'Brien and Fleming spending function, assuming 318 deaths for the final overall survival analysis.

Source: compiled during the evaluation based on data presented in Section 2.5, pp60-76 of the submission.

6.20 On the basis of direct evidence presented by the submission, for every 100 patients treated with osimertinib in comparison to erlotinib/gefitinib and followed over a maximum duration of approximately 27 months:

- Approximately 27 more patients would remain progression-free at 18 months;
- Approximately 12 more patients would remain alive at 18 months;
- Approximately 11 fewer patients would experience a Grade≥3 adverse event;
- Approximately 4 fewer patients would experience a serious adverse event. However this difference is not statistically significant which may be due to insufficient statistical power of the analysis; and
- Approximately 4 fewer patients would experience an adverse event leading to discontinuation of study treatment. However, this difference is not statistically significant which may be due to insufficient statistical power of the analysis.

6.21 The PBAC noted that an additional benefit of first-line treatment with osimertinib would be that patients would not be subject to a biopsy to determine T790M status prior to consideration of appropriate second-line therapy.

Clinical claim

6.22 The submission claimed that first-line treatment with osimertinib is statistically superior to erlotinib or gefitinib in terms of efficacy and QoL, and clinically superior in terms of safety in patients with locally advanced or metastatic EGFR M+ NSCLC.

6.23 The ESC and the PBAC considered the claim of superior treatment effect of osimertinib versus erlotinib/gefitinib in terms of PFS was reasonable, based on the evidence presented in FLAURA.

6.24 The ESC and the PBAC considered the OS benefit associated with first-line osimertinib compared with early-generation TKIs in treating EGFR M+ NSCLC was inconclusive. This was due to the immaturity of the OS data and the potential overestimated OS benefit in the osimertinib arm due to the likely underuse of second-line osimertinib post-progression in the comparator arm compared with clinical practice.

6.25 Although patients receiving osimertinib had statistically significant improvement in the symptom of chest pain and in social, emotional and cognitive functioning compared with those in the comparator erlotinib/gefitinib arm, the differences between the two intervention groups did not meet the pre-specified clinically relevant cut-off of ≥10 points, defined in the FLAURA trial protocol.

6.26 The clinical evidence showed that osimertinib was associated with reduced incidence of ≥ Grade 3 AEs, serious AEs and discontinuation due to AEs, compared with erlotinib/gefitinib, although the differences were not always statistically significant (likely due to the insufficient statistical power of the AE analyses). However, the proportions of patients experiencing ILD or ILD-like events, QT prolongation and reduced LVEF were numerically higher in patients receiving osimertinib than those in the comparator erlotinib/gefitinib arm. This is consistent with the known safety profile of osimertinib. On balance, the ESC considered that osimertinib appeared to be more tolerable than the early generation TKIs; accordingly, the ESC considered the claim of superior safety compared with erlotinib or gefitinib was reasonable.

6.27 The PBAC considered that the claim of superior comparative safety was reasonable.

Economic analysis

6.28 The submission presented a modelled economic evaluation based on the FLAURA trial. The type of economic evaluation was a cost-utility analysis. The key components of the economic evaluation are summarised below.

Table 9: Summary of model structure and rationale

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	LYs and QALYs
Time horizon	10 years in the model vs. 25 months[a] in the FLAURA trial
Methods used to generate results	Partitioned survival cohort analysis
Health states	Three: PFS, progressive disease and death
Cycle length	30 days
Allocation to health states	The proportion of patients in each health state was determined by the PFS and OS curves.
Extrapolation method	The PFS and OS estimates observed from the FLAURA trial were applied to the economic model until the extrapolation time point[b]. Parametric distributions fitted to the observed Kaplan-Meier survival estimates were used to extrapolate PFS and OS to the end of the time horizon of the model, with the independent Weibull distribution selected in the base case for OS and the dependent generalised gamma function for PFS. Convergence was not assumed to occur within the modelled time horizon. 75.4% of incremental QALYs (and 0.2% of incremental costs) occur in the extrapolated period.
Utilities	EORTC QLQ-C30 from the FLAURA trial, mapped to EQ-5D. PFS = [redacted] for osimertinib arm, [redacted] for erlotinib/gefitinib arm Progressive disease = [redacted] in both arms
Software package	Excel 2016

EGFR M+ = epidermal growth factor receptor mutation positive; EORTC QLQ-C30 = European organisation for research and treatment of cancer quality of life questionnaire – core 30 items; EQ-5D = EuroQol – 5 dimensions; LY = life-year; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life-year; TKI = tyrosine kinase inhibitor

[a] Corresponds to the latest time point which observed PFS and OS data were available for both osimertinib and gefitinib/erlotinib arms

[b] PFS trial data were used up to 19 months for osimertinib arm and 11 months for erlotinib/gefitinib arm, OS trial data were used up to 15 months for both arms.

Source: Table 3.1-1, p92 of the submission.

6.29 The key drivers of the model are summarised in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
Treatment cost for first-line osimertinib	[redacted] packs (of 30 x 80mg tablets) per patient based on truncated mean treatment duration from FLAURA in which 51% of patients were still receiving treatment at end of reported follow-up.	High, favoured osimertinib
OS extrapolation	Treatment effect continued beyond 25-month trial period for up to 10 years with no convergence	High, favoured osimertinib
Time horizon	10 years (compared with 25 months in the FLAURA trial)	High, favoured osimertinib
The extent of use of later-line osimertinib in the comparator arm	58.8% of patients who discontinued erlotinib or gefitinib – cost of the later-line osimertinib in these patients were considered, but not the associated health benefit	Moderate, favoured osimertinib

Source: Compiled during the evaluation based on Section 3.9 of the submission and the sensitivity analyses performed during the evaluation.

6.30 The results of the economic evaluation are summarised in Table 11. As 34% of patients received erlotinib and the remaining 66% were treated with gefitinib in the FLAURA trial, the economic model assumed the same relative use of erlotinib and gefitinib in clinical practice and applied weighted cost of $1,378.56 for comparator erlotinib/gefitinib per 30-day cycle. On 1 April 2019, there was a price reduction for both erlotinib and gefitinib. During the evaluation of the economic model, the results of the economic evaluation were updated using the updated cost for erlotinib as the

drug cost for comparator EGFR-TKI (see the revised base case in Table 10). This was based on: 1) erlotinib is the most commonly used TKI agent in current clinical practice (around 70%); 2) erlotinib is less costly than gefitinib (dispensed price for maximum quantity (DPMQ): $1,151.62 vs. $1,270.98, respectively); and 3) erlotinib and gefitinib (and afatinib) are considered interchangeable at a per-patient level.

Table 11: Results of the stepped economic evaluation

Step and component	Osimertinib	Erlotinib/gefitinib	Increment
Step 1: trial-based, time horizon of 25 months, cost for first-line therapy only			
Costs			
LYs gained			
Incremental cost/extra LY gained			
Step 2: time horizon extended to 10 years			
Costs			
LYs gained			
Incremental cost/extra LY gained			
Step 3: incorporation of costs for health care resource use			
Costs			
LYs gained			
Incremental cost/extra LY gained			
Step 4: utility weights applied			
Costs			
QALYs			
Incremental cost/extra QALY gained (base case)			
Revised based case using the updated erlotinib price[a]			
Costs			
QALYs			
Incremental cost/extra QALY gained (Revised base case)			

LY = life-year; QALY = quality-adjusted life-year

[a] Revised during the evaluation by using the updated erlotinib price ($1,151.62) as the drug cost for erlotinib/gefitinib in the comparator arm and by correcting the cost for carboplatin+gemcitabine in the later-line setting.

Source: Table 3.8-1, p135 of the submission.

The redacted table shows ICERs in the range of $45,000-$75,000/QALY.

6.31 The submission argued that the time to treatment discontinuation (TTD) from the FLAURA trial included treatment breaks and therefore overestimated the actual treatment duration. Therefore in the model, the cost of first-line osimertinib was estimated by assuming an average of [redacted] packs (of 30 x 80mg tablets) dispensed per patient, as the actual mean osimertinib exposure time (AET) (excluding period of dose interruption) in the FLAURA trial was [redacted] months, resulting in an average cost per course of $100,000-$200,000 . In contrast, the duration of treatment with first-line erlotinib/gefitinib was determined by the proportion of patients remaining on treatment in each cycle (from extrapolated TTD curve).

- The evaluation considered that the different approach to estimating the duration of the treatment in each arm introduced bias in favour of first-line osimertinib. The mean treatment duration reported in FLAURA was effectively the truncated mean, because at the June 2017 data cut-off, 50.5% patients in the osimertinib arm and 23.1% in the erlotinib/gefitinib arm were still receiving their randomised treatment.

Extrapolating the health benefits (i.e. PFS and OS) associated with first-line osimertinib but not the costs resulted in an ICER favouring osimertinib. The evaluation found that if the extrapolated TTD for osimertinib was used in estimating the treatment duration, in line with first-line erlotinib/gefitinib in the comparator arm, the treatment duration would be [redacted] months and the average cost per course would be $100,000 -$200,000 . This resulted in the ICER doubling from $45,000 -$75,000/qaly gained in the base case to $105,000-$200,000/QALY gained (see scenario #7 in Table 12).

- The PSCR acknowledged that the truncated mean was used in the analysis; however, the PSCR claimed that the extrapolated TTD curve overestimated the duration of treatment, and therefore the cost of osimertinib, and was therefore not appropriate. The PSCR suggested it would be reasonable to assume that there is a relationship between the truncated AET ([redacted] months) and truncated TTD based on the Kaplan-Meier curve ([redacted] months), where the ratio of these two parameters (0.78) could be used to estimate the mean actual exposure time (AET) over the modelled TTD for osimertinib. By applying the AET/TTD ratio to the extrapolated TTD curve for osimertinib ([redacted] months), the mean AET is [redacted] months. Based on this estimate, the ESC calculated the cost of a course of treatment with osimertinib increased from $[redacted] to $[redacted] and the corresponding ICER would increase from $45,000-$75,000 /QALY gained to $105,000-$200,000 /QALY gained.
- [redacted], the PSCR stated the total cost of treatment will be limited to [redacted] as part of an RSA and, in this context, the approach to estimating the cost of treatment with osimertinib and hence the result of the cost-effectiveness analysis in the submission was valid. The ESC noted that the submission did not provide any details of a proposed RSA for first-line osimertinib.
- The ESC considered that given the treatment length was likely to be underestimated in the model in the submission, the costs for health care resource use was also likely to be underestimated. Overall, the ESC considered it would have been more appropriate for the treatment duration to be estimated based on the extrapolated TTD curve.
- The pre-PBAC response provided further details regarding the proposed RSA and presented a respecified base case where the average treatment duration for osimertinib was intended to be capped at [redacted] packs (or less than $10 million per patient). As such, the pre-PBAC response considered the need to use extrapolated TTD to inform the cost of osimertinib was negated. However, the PBAC noted that the use of subsidisation caps through an RSA is associated with a significant risk that the Government would pay a higher amount less than $10 million per patient. This is because realisation of this [redacted] is achieved only via subsidisation caps and is therefore dependent on the estimated utilisation being met or exceeded.

6.32 The evaluation considered that the modelled OS data based on the FLAURA trial may not be an adequate reflection of the clinical benefit of first-line osimertinib in clinical practice for the following reasons:

- Trial data did not provide a reliable basis for extrapolation of OS given the immaturity of the OS data (only 20.8% patients in the osimertinib arm and 30.0% of patients in the erlotinib/gefitinib arm had died by the data cut-off); and
- The potential underuse of second-line osimertinib in the comparator arm in FLAURA compared with that in clinical practice would have underestimated the OS benefit of patients in the comparator arm. The ESC noted that the model did not attempt to adjust the OS benefit of the comparator arm.
- Overall, the ESC considered the comparator arm of the model was not reflective of current standard care.

6.33 Although the model did not consider the additional OS benefit in the comparator arm from the increased use of second-line osimertinib in clinical practice, the costs of an increased use of later-line osimertinib compared with that reported in FLAURA were included. The submission assumed 58.8% of patients discontinuing erlotinib/gefitinib would receive second-, or third-line osimertinib (vs. 29.1% in the trial). The ESC considered this may be an overestimate, given the 60% prevalence of T790M mutation among patients eligible for biopsy, and the fact that some patients would not be eligible for later-line osimertinib due to their poor performance status following disease progression. Accordingly, the ESC considered this assumption biased the results of the economic evaluation in favour of first-line osimertinib.

- As noted in paragraph 6.12, the PSCR argued that 48.1% of patients in the comparator arm who commenced treatment with a second-line therapy received osimertinib and that as the FLAURA clinical trial continues, and more patients have the opportunity to commence second-line treatment, this proportion is expected to increase further. As such, the PSCR claimed that use of second-line osimertinib in the comparator arm of the FLAURA clinical trial is likely to correspond to that observed in clinical practice.
- The ESC noted that as the proportion of 48.1% represented the extent of use of osimertinib among all subsequent therapies, it was not relevant to the modelled economic evaluation. The ESC discussed this was because the cost of later-line osimertinib in the model was applied to the proportion of patients who discontinued randomised treatment (assumed to be 58.8% in the model, in spite of an observed proportion of 29.1% in the trial). The economic model assumed that 82% of patients who discontinued randomised treatments will receive second-line therapies (compared with 60% in FLAURA) and 48% of those who discontinued randomised treatment will further receive a third-line treatment.

6.34 The submission assumed that, after the trial observation period, the survival curves would follow the chosen dependent parametric functions continually until the end of the model duration. The evaluation considered this assumption was not justified, particularly considering that most of the model period (8 out of 10 years) is unobserved. The PBAC guidelines (Version 5.0) state that "if the treatment effect is maintained or increasing, and this is not clinically plausible, apply a hazard ratio such that the intervention and comparator curves converge at a plausible time point" . Of all the parametric distributions for OS extrapolation in the model, the evaluation considered the dependent Gompertz model provided the most conservative survival estimates for both treatment arms and was the only parametric function with the OS curves converging within the model time horizon (see Figure 4). Sensitivity analyses performed during the evaluation showed that the model results are sensitive to the choice of parametric function for the OS extrapolation; when the dependent Gompertz extrapolation method was used, the ICER increased from $75,000 to $105,000 /QALY gained (see scenario #4 in Table 12).

- The PSCR stated that the Gompertz distribution had the worst statistical fit based on the AIC and BIC statistics. The ESC considered that the AIC and BIC statistics did not differ greatly across parametric distributions and visual inspection indicated that all parametric models, with the exception of the exponential distribution, appeared to fit the observed OS data well.

- The PSCR further claimed that, "the modelled OS curve using a Gompertz distribution for SoC is significantly below the long-term OS data from the study by Lin et al 2016, which enrolled patients with predominantly Stage IV disease treated with a first-line EGFR-TKI. Given that the patients in the study by Lin et al 2016 have more severe disease compared to those proposed for listing of osimertinib (Stage IIIB/IV), it is not clinically plausible that the modelled survival curves for SoC is so far below that reported by Lin et al 2016". The ESC noted that Lin et al 2016 recruited patients who had Stage IV disease (77.4%) or Stages I-III disease with subsequent systemic relapse (22.6%) and received gefitinib or erlotinib for EGFR M+ adenocarcinoma. EGFR-TKI were used as first-line (67.9%), second-line (27.7%) or later-line (4.4%) therapy. The study setting of Lin et al 2016 may not reflect the circumstance of use of first-line erlotinib/gefitinib. In addition, the results were subject to bias due to its retrospective, non-comparative study design. Of note, OS data from the Lin et al 2016 study were consistently higher than those in the other two erlotinib trials (Wu 2015 and Zhou 2015). The most conservative extrapolation method of Gompertz returns OS estimates for erlotinib/gefitinib more comparable to these two erlotinib trials.

- Overall, the ESC considered that the selection of dependent Weibull distribution to extrapolate OS curves in the submission favoured first-line osimertinib, compared with erlotinib/gefitinib, up to the end of the time horizon. Accordingly, the ESC considered a more conservative choice would have been to use the Gompertz

distribution or to apply a hazard ratio such that the intervention and comparator curves converged at a plausible time point.

Figure 4: Comparison of the KM estimates for overall survival from the FLAURA trial with the independent Weibull distribution and independent Gompertz distribution

Erl/Gef = erlotinib/gefitinib; KM = Kaplan Meier; Osi = osimertinib
Source: Figure constructed during the evaluation, based on the "3. Tagrisso (osimertinib)_Economic Evaluation (Section 3)" excel workbook

6.35 The time horizon of the base case economic model was 10 years. A 10-year time horizon was substantially longer than the maximum duration of follow-up in the key trial (around 27 months) and was twice the time horizon of the economic models in other PBAC submissions for the same class of treatment and the same population (first-line TKIs for treatment of EGFR M+ NSCLC) (5 years). The evaluation therefore considered that the use of a 5-year time horizon may have been more appropriate, particularly given the submission's assumption of an ongoing survival benefit of first-line osimertinib throughout the model time horizon, which was not adequately justified in the submission. While some patients may be alive beyond 5 years, the evaluation noted that extrapolation of immature trial data to 10 years substantially increased the uncertainty with the cost effectiveness estimates.

- The PSCR noted the PBAC accepted a 7.5 year time horizon for pembrolizumab for the treatment of Stage IV NSCLC (Pembrolizumab PSD November 2017). The PSCR argued that since osimertinib is proposed for listing for patients with locally advanced or metastatic (Stage IIIb/IV) NSCLC, a less severe population compared to the population for pembrolizumab, a 10-year time horizon was reasonable.
- The ESC noted that when the pembrolizumab (NSCLC) submission was reviewed, the PBAC considered a longer time horizon of 7.5 years acceptable in light of the respecified model assumptions including, but not limited to, the use of a conservative parametric distribution for survival extrapolation and the

convergence of the survival curves of the two treatment arms at the end of the 7.5-year time horizon (Pembrolizumab PSD, November 2017 PBAC meeting).

- As noted above, the osimertinib submission modelled ongoing survival benefit of first-line osimertinib throughout the model time horizon of 10 years. The ESC noted that around 75% of incremental QALYs are accumulated in years 3-10 of the model. The ESC considered the use of a 5-year time horizon, in conjunction with a more conservative parametric distribution for survival extrapolation and the convergence of the survival curves of the two treatment arms at the end of the 5-year time horizon, would be more reasonable and consistent with previous submissions for first-line TKIs for treatment of EGFR M+ NSCLC.

6.36 The results of the key sensitivity analyses are summarised in Table 12.

Table 12: Results of the key sensitivity analyses[a]

	Costs			QALYs			ICER
	Osi	Erl/Gef	Increment	Osi	Erl/Gef	Increment	($/QALY)
Revised base case[a]	$	$					$
Time horizon (base case: 10 years)							
1. 5 years[b]							
2. 7.5 years							
3. 15 years							
OS extrapolation method (base case: dependent Weibull distribution)							
4. Gompertz distribution[b]							
5. Log-logistic distribution							
6. Log-normal distribution							
Drug cost for osimertinib (base case: 14.9 packs per patient)							
7. Extrapolated TTD curve (packs)[b]							
Subsequent use of osimertinib in the comparator arm (base case: 58.8% in second-line and third-line combined)							
8. 29.1% based on Trial FLAURA[b,c]							
Multivariate sensitivity analyses							
#1 + #4[b]							
#1 + #7[b]							
#1 + #8[b]							
#1 + #4 + #7[b]							
#1 + #4 + #7 + #8[b]							

Erl/Gef = erlotinib/gefitinib; ICER = incremental cost-effectiveness ratio; OS = overall survival; Osi = osimertinib; QALY = quality-adjusted life-year; TTD = time to treatment discontinuation

[a] Analyses performed using the updated erlotinib price ($1,151.62) as the drug cost for erlotinib/gefitinib in the comparator arm and correcting the cost for carboplatin+gemcitabine in the later-line setting.

[b] Sensitivity analyses not considered in the submission

[c] In the FLAURA trial, a total of 62 patients randomised to the erlotinib/gefitinib arm received subsequent osimertinib therapy, representing 29.1% (62 out of 213) of patients who discontinued randomised treatment. This proportion was used in the sensitivity analysis. The proportions of patients receiving other subsequent anti-cancer therapies were re-distributed proportionally, e.g. 73.4% for carboplatin+gemcitabine, 27.2% for pemetrexed and 0.3% for nivolumab.

Source: Sensitivity analysis performed during the evaluation, using "3. Tagrisso (osimertinib) _ Economic Evaluation (Section 3)" excel workbook

6.37 The ESC considered that there were several assumptions in the economic model that favoured first-line osimertinib, compared with early-generation TKIs. The ESC

considered that a multivariate sensitivity analysis with the following changes would provide a more reasonable estimate of the ICER than the (revised) base case in the submission:

- a 5 year time horizon;
- a more conservative choice of function (such as the Gompertz distribution) for OS extrapolation and apply a hazard ratio such that the intervention and comparator curves converge by the end of the time horizon; and
- the extrapolated TTD curve for estimating the cost of osimertinib.

The ESC considered this multivariate scenario may still favour osimertinib given the potential underuse of second-line osimertinib in the comparator arm of FLAURA, compared with clinical practice, and the potential overestimate of the costs of second-line osimertinib. The ESC noted that updated OS data that is to become available towards the end of 2019 may reduce the uncertainty in the benefits of osimertinib in first-line treatment.

6.38 The pre-PBAC response provided a revised base case with the following assumptions:

- A 7.5 year time horizon;
- Weibull function for OS was maintained. However, a sensitivity analysis was presented in the pre-PBAC response using the Gompertz function;
- a linear decline in the covariate for osimertinib in the dependent Weibull function from 5 years to a covariate of nil at 7.5 years; and
- the average treatment duration for osimertinib per patient which is intended to be capped at [redacted] packs (or less than [redacted]), to be implemented through subsidisation caps through an RSA.

The revised base case resulted in an ICER of $45,000-$75,000 /QALY gained. The pre-PBAC response also presented a sensitivity analysis in which OS was estimated using a Gompertz function; in this scenario, the ICER increased to $45,000-$75,000/QALY gained.

Drug cost/patient/course

6.39 The per patient drug costs for osimertinib and early-generation TKIs are presented in Table 13. The cost for osimertinib in the submission's economic evaluation was calculated by assuming [redacted] osimertinib packs dispensed per patient. The drug cost of osimertinib would increase to less than $10 million (compared with less than $10 million in the base case), if the extrapolated TTD curve from the FLAURA trial was used. By comparison, the average cost per patient for a course of treatment with second-line osimertinib is currently intended to be limited to less than $10 million (implemented through an RSA in the form of subsidisation caps). The pre-PBAC

response proposed the RSA subsidisation caps could be limited to less than $10 million , based on a [redacted] month treatment course for first-line osimertinib therapy. As noted above the PBAC considered that the use of subsidisation caps through an RSA is associated with a significant risk that the Government would pay a higher amount less than $10 million per patient

6.40 The drug cost for erlotinib was estimated to be [redacted], using the updated erlotinib DPMQ and the modelled TTD curve.

Table 13: Drug cost per patient for osimertinib and comparator (other first generation TKIs)

	Osimertinib			Erlotinib/gefitinib/afatinib		
	Trial dose and duration	**Model**	**Financial estimates**	**Trial dose and duration**	**Model**	**Financial estimates**
Mean dose	80mg/day[a]	80mg/day	80mg/day	Erl: 150mg/day[a] Gef: 250mg/day[a]	Erl: 150mg/day Gef: 250mg/day	Erl: 150mg/day Gef: 250mg/day Afa: 40mg/day
Mean duration	[redacted] months (truncated actual mean duration)[b]	[redacted] months[c]	[redacted] months (truncated total mean duration)[d]	[redacted] months (truncated actual mean duration)[b]	[redacted] months[c]	[redacted] months (truncated total mean duration)[d]
Cost/patient/month	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost/patient/course	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Afa = afatinib; Erl = erlotinib; Gef = gefitinib; TKI = tyrosine kinase inhibitor

[a] Dose regimens in FLAURA trial. The mean doses for osimertinib, erlotinib and gefitinib were not reported. However, the clinical study reported that there was a low proportion of patients in both arms who had dose reduction (6.1% in the osimertinib arm vs. 6.9% in the gefitinib/erlotinib arm).

[b] Truncated actual mean duration (excluding dose interruption period). At the data cut-off, 50.5% (141/279) in the osimertinib arm and 23.1% (64/277) in the erlotinib/gefitinib arm were ongoing on their randomised treatment.

[c] Calculated by the total drug cost from the economic model (undiscounted) divided by the dispensed price for maximum quantity (DPMQ) (30-day treatment supply)

[d] Truncated total mean duration (including dose interruption period). At the data cut-off, 50.5% (141/279) in the osimertinib arm and 23.1% (64/277) in the erlotinib/gefitinib arm were ongoing on their randomised treatment.

[e] When the submission was prepared, the DPMQs were $1,270.98 for erlotinib (30-day therapy) and $1,433.74 for gefitinib (30-day therapy). The drug cost in the comparator arm was weighted assuming 34% of patients receiving erlotinib and 66% receiving gefitinib as in Trial FLAURA.

[f] Drug cost calculated by assuming 100% using erlotinib and using the current erlotinib price after 10% statutory price reduction (DPMQ: $1,151.62)

[g] In the financial analysis, the drug cost in the comparator was weighted on the basis of the available PBS data on TKIs: 70.8% erlotinib, 28.4% gefitinib and 0.8% afatinib. The DPMQs used in the submission were $1,270.98 for erlotinib (30-day therapy), $1,433.74 for gefitinib (30-day therapy), and $1,343.32 for afatinib (28-day therapy).

[h] Drug cost/patient/course was calculated by multiplying the cost/patient/month with the mean actual duration of treatment (excluding period of dose interruption) reported in FLAURA

[i] Undiscounted drug cost from the economic model

[j] Drug cost/patient/course was calculated by multiplying the cost/patient/month with the mean total duration of treatment (including period of dose interruption) reported in FLAURA

Source: Table compiled during the evaluation, based on p114 of the submission and the "3. Tagrisso (osimertinib)_Economic Evaluation (Section 3)" excel workbook

Estimated PBS usage & financial implications

6.41 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the financial implications associated with the proposed listing of osimertinib in the first-line setting. As osimertinib is expected to substitute for

existing first line listings of EGFR TKIs, a market share approach would have been more appropriate. The estimation of the population likely to be treated was based on Australian Institute of Health and Welfare (AIHW) incidence data[6], previous MSAC and DUSC advice on NSCLC submissions[7], market research data[8], and the submission's assumptions. The main uncertainties regarding the number of patients likely to receive first-line osimertinib in clinical practice were the prevalence of EGFR mutations (20% in the submission) and the uptake of osimertinib ([redacted]% in Year 1 of listing, increasing to [redacted]% in Year 6). The ESC considered that the majority of eligible patients would be treated with first-line osimertinib instead of earlier-generation TKIs; accordingly, these uptake rates may be underestimated. However, the ESC noted that if first-line osimertinib was listed with subsidisation caps through an RSA [redacted] it would be preferable to have a high degree of certainty that the utilisation estimates used to determine the subsidisation caps would be met.

6.42 The duration of therapy with osimertinib and substituted TKIs in the first-line setting was sourced from the FLAURA trial. The use of truncated mean duration of treatment from the clinical trial was not justified and biased the result in favour of first-line osimertinib, as more patients in the osimertinib arm of the trial were still receiving randomised treatment than in the comparator erlotinib/gefitinib arm at the June 2017 data cut-off (50.5% vs. 23.1%). As with the economic model, the ESC considered the treatment duration for the financial estimates should be estimated based on the extrapolated TTD curve. The pre-PBAC response presented a revised base case to align with the RSA proposal where the average treatment duration for osimertinib was capped at [redacted] packs.

6.43 In April 2019, a price reduction was applied to erlotinib and gefitinib. The updated prices were thus used during the evaluation to estimate the financial implications to the PBS/RPBS (as described in paragraph 6.30). There is a SPA in place for afatinib; the submission assumed an effective DPMQ for afatinib based on the published therapeutic relativity for afatinib, which stated that 40 mg afatinib is equivalent to 150 mg erlotinib. The financial implications may need to be updated for the effective DPMQ of afatinib.

6.44 Apart from substitution of erlotinib, gefitinib and afatinib in the first-line setting, the financial analysis included cost offsets associated with the reduced use of second-line

[6] AIHW 2012. Cancer incidence projections Australia, 2011 to 2020. Cat. no. CAN 62. Available from: https://www.aihw.gov.au/reports/cancer/cancer-incidence-projections-australia-2011-to-20/contents/table-of-contents; AIHW 2011, Cancer Australia. Lung cancer in Australia: an overview. Cat. no. CAN 58. Available from: https://www.aihw.gov.au/reports/cancer/lung-cancer-in-australia-overview/contents/table-of-contents.

[7] Application 1161 Public summary document (PSD), November 2012 MSAC meeting; Durvalumab DUSC Advice, November 2018 PBAC meeting.

[8] IPSOS 2018. Overview of the NSCLC cancer treatment landscape - 2018 Q2 IPSOS Global Oncology Monitor in Australia; QuintilesIMS 2017. AstraZeneca treatment patterns in advanced non-small cell lung cancer 2017.

osimertinib in patients who have developed an EGFR T790M resistance mutation following first-line TKIs. In the submission's base case analysis, the number of patients expected to receive second-line osimertinib was derived directly from the November 2018 osimertinib (second-line) submission. A financial analysis using the epidemiological data in the current submission was presented in the attachment to the main submission as a scenario analysis. Due to the differences in the financial inputs between the previous second-line osimertinib submission and the current submission, the number of patients receiving second-line osimertinib in the scenario analysis was twice the number of patients in the submission's base case.

6.45 The cost offsets associated with second-line osimertinib use was estimated by applying the average cost per patient of $[redacted], according to the existing RSA, to the number of patients no longer receiving treatment with osimertinib in the second-line setting. However, the average cost per patient is intended to be achieved via subsidisation caps and is therefore dependent on estimated utilisation being met or exceeded. The PBAC noted there was limited utilisation data available given osimertinib was only listed in February 2019. Therefore, the offsets for reduced use of osimertinib in the second-line treatment setting relied on previously agreed estimates for this setting.

Table 14: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of osimertinib						
Costs to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Costs to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications for other medicines						
Change in costs of erlotinib, gefitinib and afatinib to PBS/RPBS less copayments[b,d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Change in costs of second-line osimertinib to PBS/RPBS less copayments	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net financial implications[d]						
Net costs to PBS/RPBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net costs to MBS[c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net costs to PBS/RPBS/MBS	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Number of scripts per patient: [redacted] in the first year of treatment and [redacted] in the subsequent year.
[b] The costs to PBS/RPBS were revised using the updated prices for erlotinib and gefitinib.
[c] The MBS costs were revised from the submission by: 1) excluding osimertinib grandfathered patients ([redacted] in Year 1); 2) assuming 82% of patients receiving first-line erlotinib, gefitinib or afatinib TKIs are suitable for biopsy/test to determine their eligibility for second-line osimertinib; and 3) using 85% MBS benefit (non-general practitioner services provided out of hospital)
[d] Adjustments made during the evaluation
Source: Table compiled during the evaluation, based on Table 4.2.2, p152, Table 4.2.3, p153, Table 4.2.5, p154, Table 4.2.6, p155, Table 4.2.8, p156, and Table 4.3.15, p171 of the submission; the "Tagrisso (osimertinib) Predicted Use (Section 4)" excel workbook.

6.46 At year 6, the estimated number of patients was less than 10,000. The total net cost to the PBS over 6 years would be more than $100 million. Further information regarding the total costs under the RSA proposal is provided in the following section.

6.47 The PBAC considered that the epidemiological approach in the submission overestimated the population using first-line treatment compared to the actual number of patients who were dispensed PBS subsidised therapy with erlotinib or gefitinib. The PBAC considered that a market share approach would have been a more appropriate method of calculating patient numbers, as osimertinib is expected to substitute for existing first-line listings of EGFR TKIs. The PBAC considered that use of first-line osimertinib would be similar to current incident use of currently available first-line TKIs. Accordingly, the PBAC considered the estimated utilisation and financial implications in the submission to be uncertain and likely to have been significantly overestimated.

Financial Management – Risk Sharing Arrangements

6.48 A RSA, in the form of subsidisation caps, currently applies to the listing for second-line osimertinib. The subsidisation caps were determined with the intention of limiting the average cost per patient to less than $10 million in forward years; however whether this intention is achieved is dependent on the estimates of utilisation that were agreed with the sponsor and used to calculate the subsidisation caps being met or exceeded. If osimertinib is recommended for listing for first-line treatment, the majority of patients are expected to receive first-line treatment with osimertinib, rather than second-line. Therefore, if osimertinib is listed for first-line treatment, the estimates of utilisation for second-line treatment would not be met and the average cost per patient for second-line treatment would be significantly higher than the intended less than $10 million. The evaluation noted this uncertainty could potentially be mitigated by combining the two lines of treatment under the one set of subsidisation caps.

6.49 The submission did not provide any details of a proposed RSA for first-line osimertinib. The pre-PBAC response proposed a combined first- and second-line RSA as follows:

- A [redacted] rebate above the agreed subsidisation cap;
- A cap threshold based on the number of patients multiplied by the mean actual treatment duration [redacted]) reported in the CSR of the FLAURA trial;
- A reduction in the total cap threshold to account for the uncertainty in the OS extrapolation which corresponds to an average cost per patient of less than $10 million ([redacted]).

6.50 The pre-PBAC response used a stepped approach to calculate the the combined subsidiation caps which is presented in the table below.

Table 15: Proposed expenditure caps for first and second-line osimertinib

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Step 1: 1L at 15 packs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Step 2: 1L at 13 packs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Step 3: 2L after substitution	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Step 4: Proposed RSA CAP (Sum of Step 2 & 3)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Table 1 of pre-PBAC response (p3). Abbreviations: 1L = first-line; 2L = second-line

6.51 Under the proposed RSA, the total net cost to the PBS over 6 years would be more than $100 million for first-line osimertinib with no second-line offsets included. The total net cost to the PBS over 6 years would be more than $100 million when the caps for first and second-line osimertinib treatment are combined.

6.52 The PBAC was of the view that the use of subsidisation caps through a Deed of Agreement with the intention of achieving a cap on the duration of treatment per patient is associated with a significant risk that the Government would pay a higher amount per course of treatment than assumed in the economic model (of less than $10 million per patient). This is because realisation of this capped amount is intended to be achieved via subsidisation caps and therefore dependent on the estimated utilisation being achieved. As noted in paragraph 6.47, the PBAC considered that the submission significantly overestimated likely utilisation of first-line osimertinib.

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

7 PBAC Outcome

7.1 The PBAC did not recommend osimertinib for the first-line treatment of locally advanced or metastatic (Stage IIIB or IV), epidermal growth factor receptor (EGFR) mutation positive (M+), non-small cell lung cancer (NSCLC). The PBAC noted the improvement in progression free survival (PFS) associated with first-line treatment with osimertinib compared with first-line treatment with erlotinib or gefitinib. However, the magnitude of benefit in overall survival (OS) was uncertain, as the data provided were still immature. The PBAC considered the ICER was unacceptably high and uncertain at the requested price. The PBAC also considered that the proposed RSA did not adequately address the uncertainty regarding the length and cost of treatment per patient, especially as the estimated PBS population for first-line use was likely to be overestimated.

7.2 The PBAC noted there was support for the listing of first-line osimertinib for EGFR M+ NSCLC. The PBAC noted that it is likely that patients would be treated with osimertinib in preference to early generation TKIs if osimertinib was listed for first-line treatment, particularly because of its more tolerable adverse event profile. The PBAC considered

that this would result in a substantial reduction in use of erlotinib and gefitinib in this clinical space.

7.3 The PBAC noted the submission nominated erlotinib and gefitinib as the main comparators, as these are the most commonly used first-line therapies for EGFR M+ NSCLC. The PBAC noted that there are two potential populations that would be treated with first-line osimertinib, resulting in two different comparators. The first population being patients who do not have evidence of EGFR T790M mutation at the point of progression following treatment with first-line erlotinib or gefitinib, for whom platinum-based doublet chemotherapy would be the standard second-line treatment, which is the same treatment as following the proposed first-line osimertinib. Accordingly, the PBAC accepted the submission's proposed comparators of erlotinib or gefitinib for this population. The second population includes patients who have progressed on or after erlotinib or gefitinib and who have evidence of EGFR T790M mutation in tumour material at the point of progression and are eligible for PBS subsidised osimertinib as a second-line treatment. The PBAC considered that the appropriate comparator for this population is treatment with erlotinib or gefitinib followed by second-line osimertinib, as this is what would be replaced in practice. The PBAC noted the argument in the pre-PBAC response that the treatment sequence was appropriately accounted for in the modelled economic evaluation; however, the PBAC considered that the comparator arm of the model was not reflective of current standard care (see paragraph 7.12).

7.4 The PBAC considered that if osimertinib was recommended for first-line treatment, a listing where first and second-line osimertinib treatment would be combined into one "line-agnostic" restriction would be appropriate. The PBAC noted that changes to Item 73337 on the MBS Schedule, relating to a tumour tissue test to determine EGFR status for access to erlotinib, gefitinib and afatinib under the PBS, would be required to include osimertinib to the list.

7.5 The submission was based on one head-to-head trial (FLAURA) comparing osimertinib with erlotinib/gefitinib in Stage IIIB or IV NSCLC patients who had not received any prior treatment for their advanced/metastatic disease and whose tumour harboured Ex19del or L858R, either alone or in combination with other EGFR mutations. The PBAC considered the FLAURA trial was applicable to the Australian population.

7.6 The PBAC considered the claim of superior treatment effect of osimertinib versus erlotinib/gefitinib in terms of PFS was reasonable based on the evidence presented from the FLAURA trial. Based on the Kaplan Meier analysis, the PBAC noted the estimated proportion of patients alive and progression-free (investigator-assessed, Response Evaluation Criteria In Solid Tumours (RECIST)-defined) was 50.9% in the osimertinib arm and 24.4% in the erlotinib/gefitinib arm at 18 months. The median PFS was 8.7 months longer for osimertinib (18.9 months) when compared with the median PFS of the comparator arm (10.2 months). First-line osimertinib was also associated with a statistically significant reduction in the risk of disease progression or death compared with erlotinib and gefitinib, with a hazard ratio (HR) of 0.46 (95% CI:

0.37, 0.57; P<0.001). The PBAC considered this difference to be clinically meaningful. The PBAC noted that similar results were reported for PFS as determined by blinded independent central review (BICR) of the imaging (median PFS: 17.7 months vs. 9.7 months; HR: 0.46 (95% CI: 0.37, 0.57)).

7.7 The PBAC considered the OS benefit associated with first-line osimertinib compared with early-generation TKIs in treating EGFR M+ NSCLC was inconclusive. This was due to the immaturity of the OS data. The PBAC noted the unadjusted results of the interim OS analysis showed a HR of 0.63 (95% CI: 0.45, 0.88; p=0.068). This extent of improvement, however, did not reach the formal statistical significance for the interim analysis (p<0.0015, determined by the O'Brien-Fleming approach for an interim analysis). The PBAC noted that the updated OS data is expected to be available late 2019.

7.8 The PBAC noted that first-line osimertinib appeared to result in a greater improvement in patients' symptoms, functioning and global health status, compared with erlotinib/gefitinib, although the differences between the two treatment arms were not always statistically significant. None of these differences reached the clinically relevant cut-off of ≥10 points, defined in the FLAURA trial protocol.

7.9 The PBAC considered that the claim of superior comparative safety was reasonable. Osimertinib was generally well-tolerated, with a numerically lower percentage of patients having AEs leading to drug discontinuation in the osimertinib arm than in the erlotinib/gefitinib arm (13.3% vs. 17.7%) of FLAURA. The PBAC considered the pattern of AEs reported in both treatment arms of FLAURA was as expected for an advanced NSCLC patient population receiving an EGFR-TKI in the first-line setting. Safety findings in the osimertinib arm were broadly consistent with the known safety profile of osimertinib, including prolongation of QT interval, cardiac contractibility and ILD, with no new safety signal identified.

7.10 The PBAC noted the cost utility analysis based on the FLAURA trial presented in the submission and the revised base case presented in the pre-PBAC response which incorporated a 7.5 year time horizon, convergence of the survival curves for the two treatment arms by the end of the time horizon and a cap on the average treatment duration for osimertinib at [redacted]. The revised base case resulted in an ICER of $45,000-$75,000/QALY gained. The pre-PBAC response also presented a sensitivity analysis in which OS was extrapolated using the more conservative Gompertz function; in this scenario, the ICER was $45,000-$75,000/QALY gained.

7.11 The PBAC accepted the use of a 7.5 year time horizon was clinically appropriate, if it were used in conjunction with respecified model assumptions including, but not limited to, the use of a more conservative parametric distribution for survival extrapolation and the convergence of the survival curves of the two treatment arms at the end of the 7.5-year time horizon. In this regard, the PBAC considered that the Gompertz function was the more appropriate parametric distribution to use to extrapolate the immature OS data in the base case. However, the PBAC considered

there was a risk that the Government would pay a higher amount per patient than intended through the proposed [redacted] (or less than$10 million per patient), as realisation of this [redacted] through the proposed subsidisation caps would be dependent on meeting (or exceeding) the utilisation estimates that were used to calculate the subsidisation caps.

7.12 In addition, the PBAC considered that the proportion of patients receiving any subsequent therapies in the FLAURA trial was underestimated compared with what is observed in clinical practice. The pre-PBAC response acknowledged that with further follow-up of the trial the proportion of patients who receive second-line osimertinib in the comparator arm (of FLAURA) is likely to increase and more closely reflects the prevalence of the T790M mutation post-progression in clinical practice. However, the model was not changed and the OS benefit in the comparator arm remained underestimated, which biased the results in favour of first-line osimertinib (see paragraphs 6.32-33). Despite this, the cost of an increased use of later-line osimertinib compared with that reported in FLAURA was included in the economic model. The PBAC considered the submission overestimated the proportion of patients who would discontinue first-line erlotinib/gefitinib and would subsequently receive osimertinib, which also biased the results of economic evaluation in favour of first-line osimertinib. The PBAC noted the 60% prevalence of T790M mutation among patients eligible for biopsy, and the fact that some patients would not be eligible for later-line osimertinib due to their poor performance status following disease progression. Accordingly, the PBAC considered it would be reasonable to assume that the appropriate proportion of patients who would discontinue erlotinib or gefitinib who would receive later-line osimertinib in the comparator arm would be between the submission's estimate (58.8%) and the proportion within the clinical trial (29.1%). Overall, the PBAC considered that the application of benefits and costs of second-line osimertinib in the comparator arm of the model were not consistent.

7.13 Accordingly, the PBAC did not accept that the ICER based on the Gompertz function presented in the pre-PBAC response (of $45,000 - $75,000/QALY gained) would be realised in practice. Furthermore, the PBAC noted that this ICER was calculated with the capped treatment course price of less than $10 million per patient, and therefore was dependent on the utilisation numbers in the subsidisation caps being met. The PBAC considered it would have more confidence in the results of the model, if in addition to the more conservative OS parametric distribution and convergence assumptions (see paragraph 7.11), the extrapolated TTD curve for osimertinib (of [redacted] months) was used to calculate the cost of treatment with osimertinib and if the costs and benefits of second-line osimertinib were evenly accounted for in the model. The PBAC also advised that if these issues were addressed in a revised model, it may have more confidence that first-line osimertinib was acceptably cost-effective if the ICER was no more than $45,000-$75,000 /QALY gained.

7.14 The PBAC considered that the epidemiological approach in the submission overestimated the population using first-line treatment compared with the actual

number of patients who were dispensed PBS subsidised therapy with erlotinib or gefitinib. The PBAC considered that a market share approach would have been a more appropriate method of calculating patient numbers, as osimertinib is expected to substitute for existing first-line listings of EGFR TKIs. The PBAC considered that use of first-line osimertinib would be similar to current incident use of the available first-line TKIs. Accordingly, the PBAC considered the estimated utilisation and financial implications in the submission to be uncertain and likely to have been overestimated.

7.15 The PBAC noted the RSA proposed in the pre-PBAC response, which included subsidisation caps based on a [redacted] treatment course per patient (approximating an average per patient cap of less than $10 million) to account for uncertainty in the OS extrapolation, with a 100% rebate payable for Commonwealth expenditure over the caps. The PBAC agreed that if first-line osimertinib was recommended for listing, it would be appropriate to have a combined first- and second-line subsidisation cap, as a majority of patients are expected to receive first-line treatment with osimertinib, rather than second-line. However, the PBAC advised that if first-line osimertinib was listed with subsidisation caps, with the intention of capping the cost per patient per course, a high degree of certainty would be required that the utilisation estimates were reliable. In this regard, the PBAC reiterated that the estimated utilisation in the submission was uncertain and likely to be have been overestimated and the use of subsidisation caps to achieve the targeted cost per patient would therefore be associated with a significant risk that the Government would pay higher than less than $10 million per patient. Given the considerable uncertainty regarding the utilisation estimates and the immature OS data, the PBAC advised that it was not sufficiently confident that the use of subsidisation caps could be relied upon to achieve a cost-effective price. Accordingly, the PBAC advised that a substantial reduction in the requested price for osimertinib would be a more appropriate approach to achieve acceptable cost-effectiveness.

7.16 The PBAC considered that any resubmission would need to be a major submission and would need to address the following:

- provide available OS data. The PBAC noted that updated OS data will be available late 2019;
- revise the economic model to reflect any updated data, apply the more conservative parametric distribution and convergence assumptions for OS as specified in paragraph 7.11, apply a treatment length consistent with the extrapolated TTD curve for osimertinib and ensure that the second-line benefits and costs of second-line osimertinib in the comparator arm are included evenly in the model;
- reduce the requested price of osimertinib to result in an ICER of no more than $45,000-$75,000 /QALY gained; and

- revise the financial estimates and proposed RSA based on the approach outlined in paragraph 7.14 and a treatment length consistent with the extrapolated TTD curve for osimertinib.

7.17 The PBAC noted that this submission is 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.