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

1 Purpose of resubmission

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

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

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

Component	Description
Population	Treatment-naïve, locally advanced or metastatic EGFRm 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; or 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 EGFRm NSCLC, osimertinib is superior to erlotinib and gefitinib in terms of efficacy, QoL and safety.

Source: Adapted from Table 1.1.1, p16 of the resubmission.
AE = adverse event; DCR = disease control rate; EGFRm = 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

2 Background

Registration status

2.1 Osimertinib is TGA-registered 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 positive NSCLC.

Previous PBAC consideration

2.2 The PBAC previously considered osimertinib for the first-line treatment of patients with locally advanced or metastatic EGFRm NSCLC in July 2019. Table 2 summarises the key matters of concern from the previous submission and how they were addressed in the current resubmission.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addressed it
Line agnostic restriction for osimertinib	The PBAC considered a line agnostic restriction, combining first and second-line osimertinib treatment, would be appropriate (paragraph 7.4, Osimertinib PSD, July 2019 PBAC meeting).	Not addressed. The sponsor requested a separate listing for the first-line indication.
Comparator	The PBAC noted that patients who have progressed on or after erlotinib or gefitinib and who have evidence of EGFR T790M mutation in tumour material at progression would be eligible for PBS subsidised osimertinib as second-line treatment. The PBAC considered that the appropriate comparator for this population was erlotinib or gefitinib followed by second-line osimertinib (paragraph 7.3, Osimertinib PSD, July 2019, PBAC meeting) The PBAC noted the 60% prevalence of T790M mutation among patients eligible for biopsy following disease progression on erlotinib/gefitinib. It further noted that, in the comparator arm of the clinical trial, only 29.1% of patients who discontinued erlotinib or gefitinib (48% of those who received any subsequent therapy) received later line osimertinib, and considered that the comparator arm was not reflective of the current standard care (paragraph 7.3 and 7.12, Osimertinib PSD, July 2019 PBAC meeting).	While the resubmission did not specifically nominate second-line osimertinib as a component of the comparator in this patient group, the updated clinical evidence was reasonably applicable to the Australian clinical setting in this respect, given the increase in the rate of cross-over from erlotinib/gefitinib to osimertinib (see below). At the time of the updated OS analysis, only 4.7% of patients in the comparator arm were still receiving gefitinib or erlotinib; 41.3% of patients who had discontinued treatment received later line osimertinib. Of those patients in the SC arm who received any subsequent therapy, 61% received osimertinib[a]
Immature overall survival data	At the time of the previous submission, the median OS had not been reached in either treatment group in FLAURA. The PBAC considered the magnitude of the survival benefits associated with osimertinib relative to erlotinib/gefitinib as first-line therapy for EGFRm NSCLC could not be reliably estimated (paragraph 6.11, Osimertinib PSD, July 2019 PBAC meeting).	Addressed. The current resubmission presented updated survival data.

Source: Table constructed during the evaluation

[a] Out of the 109 patients who crossed over to osimertinib in the SC arm, 85 patients received osimertinib as first subsequent therapy and 24 patients as second subsequent therapy. Patients were required to have evidence of T790M mutation in tumour tissue at progression in order to receive osimertinib, however the exact prevalence of T790M mutation in the study could not be located in the resubmission.

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

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 Tablets 80mg[a]	1	30	5	$7,962.12 published price $[redacted] effective price	Tagrisso® AstraZeneca Pty Ltd
Tablets 40mg[a]	1	30	5	$7,962.12 published price $[redacted] effective price	

[a] The strength of 80mg is for both initial treatment and continuing treatment; whilst 40mg is only for continuing treatment.

Category / Program	Section 85 – General Schedule
Prescriber type	☒ Medical Practitioners
Condition	Locally advanced (Stage IIIb) or metastatic (Stage IV) non-small cell lung cancer
Treatment phase	Initial *treatment with first-line EGFR tyrosine kinase inhibitor*
Restriction	☒ Authority Required – Telephone/ Online
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 epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal.
Population criteria	Patient must have evidence *in tumour material* 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	*Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.* 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

3.2 The resubmission proposed an updated Special Pricing Arrangement (SPA), in which the proposed effective price was [redacted]% lower than in the previous submission.

3.3 Osimertinib is currently listed on the PBS for the treatment of locally advanced or metastatic NSCLC in patients who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy, and who have evidence in tumour material of EGFR T790M mutation at progression. The PBAC previously 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 (paragraph 7.4, osimertinib, Public Summary Document (PSD), July 2019 PBAC meeting). However, the resubmission requested separate restrictions for first- and second-line osimertinib, although it also stated that the sponsor was willing to

work with the Department to ensure that the wording of these listings best met the requirements of locally advanced or metastatic EGFRm NSCLC patients. The PBAC noted separate restrictions for the first- and second-line treatment settings is reasonable given the different prices for osimertinib in each setting and the expected use in each setting changing over time.

3.4 The proposed restriction in the resubmission was broader than the patient selection criteria in the key FLAURA trial in terms of: i) not limiting eligibility by tumour histology type (versus adenocarcinoma in the key trial); ii) the inclusion of patients with a performance status of 2 (versus 0 -1 only in the key trial); iii) including all patients with stage IIIB (versus specifying stage IIIB patients who are not candidates for local treatment in the key trial); and iv) the inclusion of patients who were intolerant to other TKIs that require treatment termination (which was not included in the key trial).

3.5 As in the previous submission, the resubmission proposed a minor amendment to MBS Item 73337, which is an EGFR test of tumour tissue to determine EGFR gene status for access to erlotinib, gefitinib or 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. It is expected that this revision would have no impact on the number of tests performed in clinical practice or on the cost to the MBS because an EGFR test would be required for other TKIs currently listed on the PBS, e.g. erlotinib, gefitinib and afatinib. However, there would be a reduction in the requirement for a second biopsy and testing for T790M mutation status required to determine eligibility for second-line osimertinib.

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 are diagnosed at an advanced or inoperable stage[1].

4.2 In Australia, between 15% and 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. Currently, patients who progress on

[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.

erlotinib, gefitinib or afatinib undergo a biopsy to test for the presence of T790M resistance mutation in the tumour tissue. Patients who test positive for the T790M mutation are eligible to receive PBS-subsidised osimertinib as second-line therapy.

4.3 The population proposed for treatment with osimertinib is treatment-naïve patients with locally advanced (Stage IIIB) or metastatic (Stage IV) EGFRm NSCLC.

5 Comparator

5.1 The resubmission nominated PBS listed EGFR-TKIs (represented by erlotinib or gefitinib) as the main comparator. The nominated comparator was unchanged from the previous submission.

5.2 The PBAC previously noted that there are two potential populations that would be treated with first-line osimertinib, resulting in two different comparators (paragraph 7.3 and 7.12, Osimertinib PSD, July 2019 PBAC meeting).

- The first population being patients who do not have evidence of EGFR T790M mutations at the point of progression following treatment with first-line erlotinib or gefitinib. For these patients, platinum-based doublet chemotherapy would be the standard second-line treatment, which is the same treatment as those progressing on first-line osimertinib would be likely to receive. The PBAC has accepted erlotinib or gefitinib as the appropriate comparator for this population.
- The second population includes patients who have progressed on or after erlotinib or gefitinib and who have evidence in tumour material of EGFR T790M mutation at the point of progression. These patients would be eligible for PBS subsidised osimertinib as a second-line treatment. The PBAC previously considered that the appropriate comparator for this population is treatment with erlotinib or gefitinib followed by second-line osimertinib. It further considered that the comparator arm of the model was not reflective of current standard care, since the proportion of patients receiving any subsequent therapies in the FLAURA trial (62/129, 48%) was lower than that observed in clinical practice. The PBAC noted that with a longer duration of follow up, the proportion of patients receiving subsequent therapies in the FLAURA trial (109/180, 61%) was more reflective of current standard care.

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. In addition to the longer progression free survival (PFS) and overall survival (OS) observed in the FLAURA trial, the clinician indicated one of the benefits of osimertinib was its positive effect on brain metastases and the impact that has on a patient's quality of life. The PBAC considered the hearing

provided a clinical perspective on the benefits of osimertinib in the first-line treatment setting.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (18) and organisations (3) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with osimertinib including longer PFS, OS and better tolerability than current treatments.

6.3 The PBAC noted the advice received from Lung Foundation Australia and Rare Cancers Australia clarifying the likely use of osimertinib as a first-line treatment in clinical practice. The PBAC specifically noted the advice that the use of osimertinib may improve progression free survival and overall survival with less side effects compared to current agents. The PBAC noted the advice that access to osimertinib as a first line treatment will improve the quality of life for patients with EGFRm NSCLC. 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 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)[3], based on a comparison with gefitinib/ erlotinib.

Clinical trial

6.5 The resubmission was based on one head-to-head trial (FLAURA) comparing osimertinib with erlotinib/gefitinib (representing SC) in Stage IIIB or IV NSCLC patients who had not received any prior treatment for their advanced/metastatic disease and whose tumour harboured an Ex19del or L858R EFGR mutation, either alone or in combination with other EGFR mutations (N=556). The key evidence base remained unchanged from the previous submission, except that updated OS data from the most recent data cut-off (June 2019) were presented in the resubmission.

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

Table 3: Trial and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
FLAURA	A Phase III, double-blind, randomised trial 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). Recently added publications:	DCO1: September 2017 DCO2: November 2019

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

	Ramalingam S.S. et al, Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC.	*N Engl J Med.*2020 Jan 2;382(1):41-50
	Gray J.E. et.al, Tissue and plasma EGFR mutation analysis in the FLAURA trial: Osimertinib versus Comparator EGFR tyrosine kinase inhibitor as first-line treatment in patients with EGFR-mutated advanced non–small cell lung cancer	*Clinical Cancer Research* (2019) 25:22 (6644-6652)
	Planchard D. et.al, Post-progression outcomes for osimertinib versus standard-of-care EGFR-TKI in patients with previously untreated EGFR-mutated advanced non–small cell lung cancer.	*Clinical Cancer Research* (2019) 25:7 (2058-2063)
	Cho B.C. et.al, Osimertinib versus Standard of Care EGFR-TKI as First-line Treatment in Patients with EGFRm Advanced NSCLC: FLAURA Asian Subset.	*Journal of Thoracic Oncology* (2019) 14:1 (99-106)
	Planchard D. et.al, Osimertinib vs standard of care (SC) EGFR-TKI as first-line therapy in patients (pts) with untreated EGFRm advanced NSCLC: FLAURA post-progression outcomes.	*Annals of Oncology* (2018) 29 Supplement 9
	Publications presented in the previous submission:	
	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 kinase inhibitors in patients with untreated EGFR-mutated advanced non-small-cell lung cancer.	*J Clin Oncol* 2018; 36(33): 3290-3297
	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 resubmission
DCO1 = first data cut-off (June 2017); DCO2= second data cut-off (June 2019)

6.7 The key features of the direct randomised trial are summarised in Table 4. These are largely unchanged from the previous submission, except with a longer median duration of follow up compared to the most recent data cut-off. In the current resubmission, the median duration of follow-up for OS data was 35.8 months in the osimertinib arm and 27 months in the comparator arm. These are compared with a median duration of follow-up for OS data of 18.6 months in the osimertinib arm and 17.4 months in the comparator arm, as presented in the previous submission.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
osimertinib vs. erlotinib/gefitinib						
FLAURA	556	R, DB 35.8 months	Low	Treatment-naïve locally advanced (Stage IIIB) or metastatic (Stage IV) EGFRm NSCLC	PFS, OS	Used

Source: Generated during the evaluation based on Sections 2.3 and 2.4, pp39-66 of the resubmission.
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.

Comparative effectiveness

6.8 The analysis of PFS, the primary outcome in the FLAURA trial, was conducted at the first data cut-off (June 2017). No new PFS data were provided in the resubmission. The

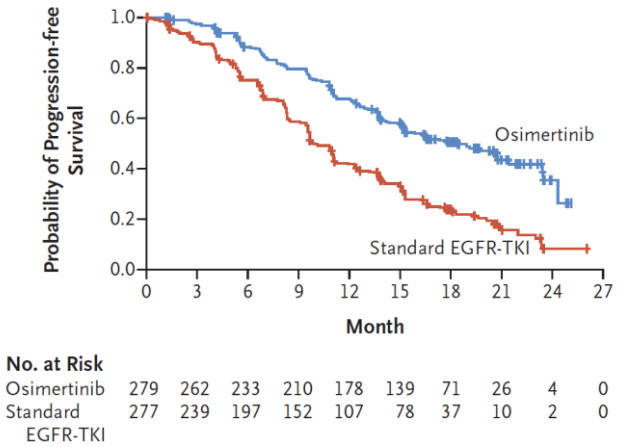
PFS results, as presented in the previous submission, are summarised again below (Table 5 and Figure 1). At the primary analysis (based on investigator assessment at time of the first data cut), the median PFS was 18.9 months and 10.2 months in the osimertinib and SC arms respectively, with an observed hazard ratio of 0.46 (95% confidence interval (CI): 0.37, 0.57).

Table 5: Results of PFS in the FLAURA trial (June 2017 data cut-off, FAS)

Event	Osimertinib	SC	Absolute Difference	HR (95% CI)
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)	8.7 months	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 24 months (95% CI)	35.8% (25.6%, 46.2%)	8.4% (3.5%, 15.9%)	27.4%	

Source: Table 2.5.2, p60 of the resubmission
CI = confidence interval; FAS = full analysis set; HR: hazard ratio; PFS = progression-free survival; SC= standard care
Median duration of follow up 15.0 months and 9.7 months in the osimertinib and erlotinib/gefitinib groups, respectively
Blue shading indicates data previously seen by the PBAC

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



Source: Figure 2.5-1, p61 of the resubmission
DCO1 = first data cut-off 1 (12 June 2017); EGFR-TKI = epidermal growth factor receptor- tyrosine kinase inhibitor; FAS = full analysis set.

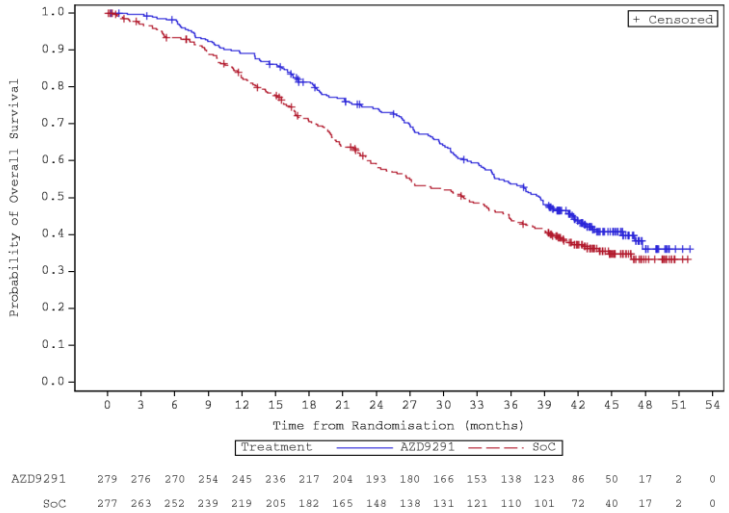
6.9 The resubmission presented updated OS data. At the second data cut-off (June 2019), the median OS was 38.6 months and 31.8 months in the osimertinib and SC arms, respectively, with a HR of 0.799 (95% CI: 0.640, 0.996). The OS data are summarised in Table 6 and Figure 2.

Table 6: Results of overall survival in the FLAURA trial, FAS

Data cut off	June 2017		June 2019	
Event	**Osimertinib**	**SC**	**Osimertinib**	**SC**
Deaths, n/N (%)	58/279 (20.8)	83/277 (30.0)	155/279 (55.6)	166/277 (59.9)
Median OS (95% CI) months	NC (NC, NC)	NC (NC, NC)	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)
Absolute difference median OS (months)	NC		6.8 months	
Hazard ratio (CI)	HR: 0.63 (99.85%CI: 0.37, 1.08)[a] P= 0.0068		0.799 (95.05%CI: 0.640, 0.996)[b] P= 0.0462	
% Alive at 12 months (95% CI)	89.1% (84.7%, 92.2%)	82.5% (77.4%, 86.5%)	89.1% (84.7%, 92.2%)	82.5% (77.4%, 86.5%)
Absolute difference at 12 months	6.6%		6.6%	
% Alive at 24 months (95% CI)	73.7% (66.4%, 79.6%)	64.7% (57.7%, 70.9%)	74.2% (68.6%, 79.0%)	58.9% (52.7%, 64.6%)
Absolute difference at 24 months	9.0 %		15.3%	
% Alive at 36 months (95% CI)	NC	NC	53.7% (47.5%, 59.5%)	44.1% (38.0%, 50.1%)
Absolute difference at 36 months	NC		9.6%	
% Alive at 48 months (95% CI)	NC	NC	36.2% (28.6%, 43.7%)	33.4% (27.1%, 39.9%)
Absolute difference at 48 months	NC		2.8%	

Source: Table 2.5.5, p65 of the resubmission and table 2.5.5, p66 of the previous submission
CI = confidence interval; FAS = full analysis set; HR = hazard ratio; NC = could not be calculated; OS = overall survival; SC = standard care.
[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
[b] The adjusted CI is computed at the 2-sided 95.05% level, considering the multiple testing with a 2-sided significance level of 0.0015 already spent at the interim overall survival analysis with 141 deaths, based on the O'Brien and Fleming spending function.
Median duration of follow up 35.8 months in the osimertinib group and 27 months in the SC group.
Blue shading indicates data previously seen by the PBAC

Figure 2: Kaplan-Meier Curve for overall survival in FLAURA trial (June 2019 data cut off, FAS)



Source: Figure 2.5.3, p66, Clinical Study Report (data cut-off 2, June 2019)
Abbreviations: EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; FAS, full analysis set

6.10 The evaluation considered the OS benefit of osimertinib compared with SC (erlotinib/gefitinib) should be interpreted with caution, given:

- A large proportion of patients continued randomised first-line treatment beyond progression (67% and 70% in osimertinib and SC arms for a median of 8 and 7 weeks, respectively). Treatment with TKIs beyond progression is not allowed in the proposed or existing PBS restrictions for the EGFR-TKIs;
- In the osimertinib arm, 69/279 (24.7%) of patients received TKIs as subsequent therapy after progression on osimertinib. Currently there is limited evidence to support the sequential use of TKIs post progression on osimertinib and it is not recommended by the National Comprehensive Cancer Network (NCCN); and
- The use of osimertinib as the first subsequent therapy after progression with first-line erlotinib/gefitinib may have been lower than would be expected in Australian clinical practice, given that, among patients who received later line osimertinib, 85/109 (78%) of them received it in the second-line setting and 24/109 (22%) received it in the third-line setting.

6.11 The ESC considered the concerns raised by the evaluation in paragraph 6.10 were reasonable but agreed with the Pre-Sub-Committee Response (PSCR) that they were unlikely to have a significant impact on the OS benefit of first-line osimertinib

6.12 Patient-reported outcomes (PROs) to assess quality of life (QoL) were only assessed at the first data cut-off. No updated data were presented in the resubmission. The PBAC previously noted that 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 arms were not always statistically significant, and that none of these differences reached the clinically relevant cut-off of ≥ 10 points, defined in the FLAURA protocol (paragraph 7.8, Osimertinib PSD, July 2019 PBAC meeting).

Comparative harms

6.13 Updated safety data were presented in the resubmission and are summarised in Table 7.

Table 7: Summary of adverse events

AE category[a]	Osimertinib N = 279 n (%)	SC N = 277 n (%)	Risk difference 95%CI	Relative risk 95%CI
Any AE	273 (97.8)	271 (97.8)	0.01% (-2.4%, 2.4%)	1.00 (0.98, 1.02)
Any AE possibly related to trial treatment [b]	253 (90.7)	255 (92.1)	1.38% (-6.0%, 3.3%)	0.99 (0.94, 1.04)
Any AE grade ≥ 3	116 (41.6)	129 (46.6)	-5.0% (-13%, 3.3%)	0.89 (0.74, 1.08)
Any AE grade ≥ 3, possibly related to trial treatment [b]	51 (18.3)	79 (28.5)	-10% (-17%, -3.3%)	0.64 (0.47, 0.87)
Any AE related death [c]	9 (3.2)	10 (3.6)	0.38% (-3.4%, 2.6%)	0.89 (0.37, 2.17)
Any AE related death, possibly related to trial treatment [b]	0	2 (0.7)	-0.7% (-1.7, 0.28%)	0
Any SAE	74 (26.5)	76 (27.4)	0.9% (-8.3%, 6.5%)	0.97 (0.74,1.27)
Any SAE possibly related to trial treatment [b]	23 (8.2)	26 (9.4)	1.1% (-5.9%, 3.6%)	0.88 (0.51, 1.50)
Any AE leading to discontinuation of trial treatment	41 (14.7)	50 (18.1)	-3.4% (-9.5%, 2.8%)	0.81 (0.56, 1.19)
Any AE leading to discontinuation of trial treatment, possibly related to trial treatment [b]	27 (9.7)	38 (13.7)	-4.0% (-9.4%, 1.3%)	0.71 (0.44, 1.12)

Source: Table 2.5.8, p71 of the resubmission

AE = adverse event; CI= confidence interval; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; SAE = serious adverse event, SC = standard of care.

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

[b] As assessed by the Investigator.

[c] Includes 1 patient (E3400004) who had pneumonia with a fatal outcome that was reported as a CTCAE grade 3 event.

Relative risk and risk difference were calculated during the evaluation, using R software.

6.14 Osimertinib was generally well-tolerated. There was a trend of a more favourable toxicity profile with the use of osimertinib compared to SC (erlotinib/gefitinib). The point estimate consistently favoured osimertinib in terms of any grade ≥ 3 adverse events, any serious adverse events, and adverse events leading to treatment discontinuation with the difference reaching statistical significance for treatment related grade ≥ 3 adverse events.

6.15 The main AEs of special interest (AESIs) were cardiac AEs including QT prolongation (10% in the osimertinib arm versus 4.3% in the SC arm) and cardiac failure (5.4% versus 2.2%). Most of the QT prolongation AEs were grade I and II. There were more grade 3 cardiac failure events in the osimertinib arm than in the SC arm (2.2% versus 0.4%). This has to be considered in the context that the key trial excluded patients with any cardiac abnormalities or those with increased risk of arrhythmic events.

6.16 As was the case in the previous submission, the pattern of AEs reported in both treatment arms of FLAURA was as expected for an advanced NSCLC patient population receiving TKIs in the first-line setting. Safety findings in the osimertinib arm were broadly consistent with the known safety profile of osimertinib, with no new safety signals identified.

Benefits/harms

6.17 A summary of benefits and harms for osimertinib versus erlotinib/gefitinib is presented in Table 8.

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

Benefits				
PFS[a] (Data cut-off June 2017)				
Event	**Osimertinib**	**SC**	**Absolute Difference**	**HR (95% CI)**
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)	8.7	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 24 months (95% CI)	35.8% (25.6%, 46.2%)	8.4% (3.5%, 15.9%)	27.4%	
Overall survival[b] (Data cut-off June 2019)				
Deaths, n/N (%)	155/279 (55.6)	166/277 (59.9)		
Median OS (95% CI) months	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)	6.8	0.799 (0.640, 0.996) P= 0.0462[c]
% Alive at 12 months (95% CI)	89.1% (84.7%, 92.2%)	82.5% (77.4%, 86.5%)	6.6%	
% Alive at 24 months (95% CI)	74.2% (68.6%, 79.0%)	58.9% (52.7%, 64.6%)	15.3%	
% Alive at 36 months (95% CI)	53.7% (47.5%, 59.5%)	44.1% (38.0%, 50.1%)	9.6%	
% Alive at 48 months (95% CI)	36.2% (28.6%, 43.7%)	33.4% (27.1%, 39.9%)	2.8%	

Harms (Data cut-off June 2019)						
	Osimertinib n/N	**SC n/N**	**RR (95% CI)**	**Event rate/100 patients**		**RD (95% CI)**
				Osimertinib	**Erlotinib/gefitinib**	
AE of grade ≥3	116/279	129 /277	0.89 (0.74, 1.08)	41.6	46.6	-5.0% (-13%, 3.3%)
Serious AEs	74 /279	76 /277	0.97 (0.74,1.27)	26.5	27.4	0.9% (-8.3%, 6.5%)
AEs leading to discontinuation of study drug	41 /279	50 /277	0.81 (0.56, 1.19)	14.7	18.1	-3.4% (-9.5%, 2.8%)

Source: compiled during the evaluation based on data presented in Section 2.5, pp59-76 of the resubmission

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; SC= standard of care.

[a] Median duration of follow up 15.0 months and 9.7 months in the osimertinib and erlotinib/gefitinib groups, respectively

[b] Median duration of follow up 35.8 months in the osimertinib group and 27 months in the SC group.

[c] The adjusted CI is computed at the 2-sided 95.05% level, considering the multiple testing with a 2-sided significance level 0.0015 already spent at the interim overall survival analysis with 141 deaths, based on the O'Brien and Fleming spending function.

Blue shading indicates data previously seen by the PBAC

6.18 On the basis of direct evidence presented by the resubmission, for every 100 patients treated with osimertinib in comparison to erlotinib/gefitinib and followed over a median duration of approximately 36 months:

- Approximately 27 more patients would remain progression-free at 24 months;
- Approximately 15 more patients would remain alive at 24 months;
- Approximately 5 fewer patients would experience a grade ≥3 adverse event;
- Approximately 1 less patient would experience a serious adverse event; and
- Approximately 3 fewer patients would experience an adverse event leading to discontinuation of study treatment.

Clinical claim

6.19 The resubmission claimed that first-line treatment with osimertinib was statistically superior to SC in terms of efficacy (PFS, OS and QoL), and clinically superior in terms of safety in patients with locally advanced or metastatic EGFRm NSCLC.

6.20 The PBAC previously considered the claim of a superior treatment effect from osimertinib versus erlotinib/gefitinib in terms of PFS was reasonable, based on the evidence presented in FLAURA.

6.21 The claim of a superior treatment effect of osimertinib compared with erlotinib/gefitinib in terms of OS was adequately supported by the updated data from FLAURA. However, the applicability of the OS results from FLAURA to Australian clinical practice remains uncertain, given that the post-progression treatments in the FLAURA trial are not consistent with the current and proposed PBS listing. This included the continued use of randomised first-line treatment with EGFR-TKIs beyond progression, the treatment with other EGFR-TKIs after progression on/after osimertinib and a proportion of patients who crossed over to osimertinib received it in the third-line setting. The ESC considered the claim that first-line treatment with osimertinib is superior to erlotinib/ gefitinib in terms of efficacy was supported by the clinical data presented in the resubmission.

6.22 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 defined in the FLAURA trial protocol of ≥10 points.

6.23 The PBAC previously considered that the claim of superior comparative safety was reasonable (paragraph 7.9, Osimertinib PSD, July 2019 PBAC meeting).

6.24 The PBAC considered that the claim of superior comparative effectiveness was reasonable, based on the updated OS data provided in the resubmission.

Economic analysis

6.25 Consistent with the previous submission, the resubmission presented a stepped economic evaluation based on updated data from the direct randomised FLAURA trial that compared first-line osimertinib with SC in patients with Stage IIIB-IV EGFRm NSCLC. The types of economic evaluation presented were a cost-effectiveness analysis and a cost-utility analysis, measuring outcomes in terms of life-years (LYs) gained and quality-adjusted life years (QALYs) gained, respectively. The key components of the economic evaluation and changes compared with the previous submission are summarised below.

Table 9: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Osimertinib vs SC (erlotinib/gefitinib) as first-line treatment
Time horizon	7.5 years in the model base case versus 25 months[a] in FLAURA (updated data were only provided for OS, for which the median follow-up was 36 and 27 months, respectively, for osimertinib and SC). This was reduced from 10 years in the previous submission. This change was consistent with the previous PBAC consideration (paragraph 7.11, Osimertinib PSD, July 2019 PBAC Meeting).
Outcomes	LYs and QALYs gained.
Methods used to generate results	Partitioned survival model (i.e. area under the curve).
Health states	Three health states: PF, PD and Dead. A change from the previous submission was that patients within the PD health state were separated, in terms of number of days until death (≥180 days, and <180 days), for the purposes of quantifying QALYs. This change had only a minor impact on the ICER.
Cycle length	30 days.
Allocation to health states and extrapolation methods	The PFS and OS KM estimates from FLAURA were used directly in the model up to the extrapolation time point[b]. Dependent parametric distributions fitted to the observed KM survival estimates were used to extrapolate PFS (Generalised Gamma) and OS (Gompertz) to the model time horizon. Convergence of the OS curves was also implemented from 24 months to ensure no difference in survival at 7.5 years. 70.5% of the incremental life-years gained were accrued in the extrapolated period. While the extrapolation time point for PFS was unchanged from the previous submission, the time point for OS extrapolation was increased from 15 to 24 months. Although an increase in the OS extrapolation time point may be reasonable given the additional data provided in the resubmission, the selection of 24 months was not justified. Median OS in FLAURA was 38.6 and 31.8 months, respectively, for osimertinib and SC, and so the selection of 24 months may not be reasonable given preference in the PBAC Guidelines for the use of observed time-to-event data over modelled data up to the point at which the observed data become unreliable. The dependent parametric model selected for OS extrapolation (Gompertz) and the implementation of OS curve convergence were additional changes made in the model relative to the previous submission. These changes were consistent with the previous PBAC consideration (paragraph 7.11, Osimertinib PSD, July 2019 PBAC Meeting).
Health related quality of life	PF utilities were mapped from the EORTC QLQ-C30 measured in FLAURA to EQ-5D (osimertinib: 0.804; SC: 0.784). PD utilities varied by time to death:

Component	Summary
	• in patients with ≥180 days to death, the same utility was applied to both treatment arms ([redacted]). This was mapped from EORTC QLQ-C30 to EQ-5D in patients with progressive disease (up to PFS2) in FLAURA • in patients with <180 days to death, a lower utility, 0.590, was applied (Chouaid 2013[4]) The PF utilities were unchanged from the previous submission. The validity and applicability of the mapping algorithm used in the economic evaluation was uncertain. However, the economic model was not sensitive to changes in health state utilities. The application of different utilities by time to death in the PD health state was a different approach to that used in the previous submission (where a single utility was applied). While no justification was provided for this change, this only has a minor impact on the ICER.

Source: Table 3.1.2, p92 of the resubmission.
EGFRm= 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; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; LY = life-year; NSCLC = non-small cell lung cancer; OS = overall survival; PD = progressive disease; PF = Progression-Free; PFS = progression-free survival; PFS2 = time from randomisation to second progression; PSD = public summary document; QALY = quality-adjusted life-year; SC = standard of care (erlotinib/gefitinib).
[a] Corresponds to the latest time point at which observed PFS and OS data were available for both osimertinib and SC arms
[b] The extrapolation time point for PFS was 19 months for osimertinib and 11 months for SC; the extrapolation time point for OS (both treatment arms) was 24 months.

6.26 In its consideration of the July 2019 submission, the PBAC identified a number of changes that would need to be made in any future resubmission (paragraph 7.13, Osimertinib PSD, July 2019 PBAC Meeting). While the resubmission adopted the majority of these suggested changes, it did not use the extrapolated time to treatment discontinuation (TTD) curve to estimate the cost of treatment with osimertinib in the base case analysis, as had been suggested. The model used the cost of [redacted] packs of osimertinib, compared with the estimated use of [redacted] packs (based on the extrapolated TTD curve). The financial estimates and caps also assume [redacted] packs per patient. Sensitivity analyses were presented in the resubmission assuming [redacted] packs of osimertinib. The ICER is highly sensitive to this change. The ESC considered it would be appropriate to include a treatment cost of [redacted] packs of osimertinib (i.e., as estimated by the TTD curve) in the economic model. The ESC considered the use of [redacted] packs to estimate the cost of treatment with osimertinib would be appropriate only if the cost per patient could be reliably capped through a Risk Sharing Arrangement (RSA).

6.27 The resubmission did not use the data from the FLAURA trial to estimate the costs of later-line osimertinib (though the health outcomes were trial-based). In the FLAURA trial, 41.3% (109/264) of patients discontinuing SC received later-line osimertinib, while the model in the resubmission applied the cost of later-line osimertinib to 75.6% of patients discontinuing first-line SC. This was derived from an assumption that 49%

[4] Chouaid C, Agulnik J, Goker E, Herder GJ, Lester JF, Vansteenkiste J, et al. Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. J Thorac Oncol. 2013 Aug;8(8):997-1003.

of patients would subsequently receive later-line osimertinib. When applied to the number of patients randomised to SC in the FLAURA trial, this was estimated to be 136 patients. While this reflects 51.5% (136/264) of patients that had discontinued SC, the denominator applied in the model was, incorrectly, the number of patients that received any treatment after randomised SC (180), and so the proportion of cost that was therefore applied on discontinuation of first-line SC modelled was 75.6% (136/180) (Table 10). This is not reasonable given that outcomes have not been similarly adjusted. The application of costs and outcomes in the model that relate to later-line osimertinib use remains inconsistent. The incremental cost-effectiveness ratio (ICER) is sensitive to the proportion of patients receiving later-line osimertinib. The ESC noted the assumption that 49% of patients would receive later-line osimertinib was consistent with that assumed for the current osimertinib second-line PBS listing which assumed that 49% of patients treated with first-line TKI inhibitors would subsequently be found to have a T790M mutation. The ESC considered it may be reasonable to use the corrected rate (51.5%) in the base case analysis but noted the use of this estimate potentially resulted in the cost offsets being inconsistent with the health outcomes in the FLAURA trial.

Table 10: A comparison of later-line osimertinib use in FLAURA and as used in the economic evaluation

	SC FLAURA N = 277	SC model arm
Patients that discontinue randomised treatment	264 (100%)	100%
Patients that receive any subsequent treatment	180 (68.2%)	68.2% [180/264]
Total patients that receive later-line osimertinib Revised	109 (41.3%)	75.6% [136/180] 51.5% [136/264]

Source: Complied during the evaluation from Table 8, pp39-40 and p39 of Clinical Study Report (data cut-off 2, June 2019), and the 'Tagrisso (osimertinib) Economic Evaluation_July 2020 PBAC meeting.xlsm' workbook.
Note: Percentages are presented as a proportion of those that discontinue first-line treatment, as these estimates are applied in the model on discontinuation of first-line treatment.
SC = standard of care (erlotinib/gefitinib).

6.28 In the base case analysis, the resubmission used the updated Kaplan-Meier data from the FLAURA trial until 24 months. At this time point the proportion of patients followed was 69.2% (193/279) in the osimertinib arm and 53.4% (148/277) in the SC arm. The resubmission did not justify the selection of this time point. Median OS in FLAURA was 38.6 and 31.8 months, respectively, for osimertinib and SC, and so the selection of 24 months may not be reasonable given preference in the PBAC Guidelines for the use of time-to-event data over modelled data up to the point at which the observed data become unreliable. The ESC considered extrapolation from median survival for osimertinib and SC would be appropriate for the base case analysis.

6.29 Beyond this time point, OS data were extrapolated using parametric functions over the modelled time horizon. The modelled health outcomes compared against the trial data that informed the efficacy inputs are presented below. On visual inspection, the dependent parametric models do not appear to fit the observed data well, particularly after the extrapolation time point of 24 months. Consequently, the modelled OS appeared to have underestimated SC survival from month 30, which would bias the

result in favour of osimertinib. The difference between the osimertinib and SC treatment arms in survival modelled at 48 months (9.5%) was substantially higher than the difference in treatment arms reported in the 48-month landmark analysis of the FLAURA trial (2.8%).

Figure 3: Kaplan-Meier and modelled curves for PFS and OS

Source: Constructed during the evaluation from 'Results' worksheet from the 'Tagrisso (osimertinib) Economic Evaluation_July 2020 PBAC meeting.xlsm' workbook included in the resubmission.
KM = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; SC = standard of care (erlotinib/gefitinib)

6.30 The key drivers of the model are summarised below.

Table 11: Key drivers of the model

Description	Method/Value	Impact
Cost of first-line osimertinib	Applied a cap on osimertinib utilisation based on the updated median duration of treatment observed in the FLAURA trial.	High, favours osimertinib (ICER increases from $105,000/QALY - $200,000/QALY[a] in the base case, to $105,000/QALY - $200,000/QALY (67% increase) when utilisation is based on the extrapolated TTD curve)
Time point for OS extrapolation	24 months	Moderate, favours osimertinib (ICER increases from $105,000/QALY - $200,000/QALY [a] to $105,000/QALY - $200,000/QALY (8% increase) when extrapolation is modelled from median OS (38.6 and 31.8 months, respectively, for osimertinib and SC)
Proportion of patients receiving later-line osimertinib in the SC arm (applied as a one-off cost on discontinuation of first-line treatment)	51.5% (proportion of patients that discontinue SC and receive subsequent osimertinib)	Moderate, favours osimertinib (ICER increases from $105,000/QALY - $200,000/QALY [a] to $105,000/QALY - $200,000/QALY (10% increase) when use from the trial is assumed (41.3%).

Source: Compiled during evaluation based on sensitivity analyses conducted during the evaluation.
ICER = incremental cost-effectiveness ratio; OS = overall survival; SC = standard of care (erlotinib/gefitinib); TTD = time-to-treatment discontinuation
[a] Revised base case ICER, excluding the additional rebate [redacted]. The base case was revised during the evaluation to reflect the cost of erlotinib only in the first-line treatment costs, 4 treatment cycles of carboplatin + gemcitabine, rather than 5.7; and reduced the proportion of patients that receive later-line osimertinib from 75.6% (i.e. 136/180) to 51.5% (136/264).

6.31 The resubmission weighted the average cost of SC by the current market share of erlotinib (67.8%) and gefitinib (32.2%). The weighted cost applied per model cycle was $1,190.17. During the evaluation, additional analyses were presented assuming only the cost of erlotinib for the cost of SC, given that: i) erlotinib is the most commonly used TKI agent in current clinical practice; ii) erlotinib is less costly than gefitinib; and iii) that the PBAC have previously considered erlotinib and gefitinib (and afatinib) are clinically non-inferior (Section 12, gefitinib PSD, July 2013). The ESC noted using a price of $1,190.17 as proposed in the resubmission (rather than $1,151.77) decreased the ICER from $105,000/QALY - $200,000/QALY to $105,000/QALY - $200,000/QALY.

6.32 The resubmission additionally proposed a rebate of $[redacted], which was applied as an additional discount to the cost per cycle of first-line osimertinib. Analyses including and excluding this additional rebate are presented below.

6.33 Additionally, the resubmission's base case analyses were revised during the evaluation to:

- Use only the cost of erlotinib for comparator EGFR-TKI cost in the analysis ($1,151.77);
- Apply four treatment cycles of platinum-doublet chemotherapy, as opposed to four model cycles (i.e. 5.7 treatment cycles) in the resubmission; and
- Correct the denominator used to estimate the total proportion of later-line osimertinib use (i.e. as a proportion of those that discontinue treatment, as it is

applied in the model, 51.5% [136/264], compared to as a proportion of those that uptake subsequent treatment, 75.6% [136/180]).

6.34 The results of the stepped economic evaluation are summarised below.

Table 12: Results of the stepped economic evaluation (revised as outlined in paragraph 6.33)

	Including the additional rebate ($[redacted])			Excluding the additional rebate		
	Osimertinib	SC	Increment	Osimertinib	SC	Increment
Step 1 – Trial based economic evaluation based on the results from FLAURA to 25 months						
Total cost [a]	$[redacted]	$16,043	$[redacted]	$[redacted]	$16,043	$[redacted]
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost per LY gained [a]			$[redacted]			$[redacted]
Step 2 – Extrapolation to 7.5 years						
Total cost [a]	$[redacted]	$18,653	$[redacted]	$[redacted]	$18,653	$[redacted]
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost per LY gained [a]			$[redacted]			$[redacted]
Step 3 – Including all resource utilisation costs						
Total cost [b]	$[redacted]	$71,893	$[redacted]	$[redacted]	$71,893	$[redacted]
Total LYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost per LY gained [b]			$[redacted]			$[redacted]
Step 4 – Transformation of health outcomes into QALYs						
Total cost [b]	$[redacted]	$71,893	$[redacted]	$[redacted]	$71,893	$[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Incremental cost per QALY gained [b]			$[redacted]			$[redacted]

Source: Constructed during the evaluation from Table 3.8.1, p144 of the resubmission and the 'Tagrisso (osimertinib) Economic Evaluation_July 2020 PBAC meeting.xlsm' workbook.

ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality-adjusted life year; SC = standard of care (erlotinib/gefitinib)

Note: The resubmission base-case analysis included an additional rebate of $[redacted]. Analyses are presented including and excluding this additional rebate.

[a] In Steps 1 and 2, costs were revised during the evaluation to reflect the cost of erlotinib only in the first-line treatment costs.

[b] In Steps 3 and 4, in addition to using the cost of erlotinib as the cost of first-line SC, the cost of subsequent therapy was revised during the evaluation to reflect 4 treatment cycles of carboplatin + gemcitabine, rather than 5.7; and the proportion of patients that discontinue first-line SC and receive later-line osimertinib was reduced from 75.6% (i.e. 136/180) to 51.5% (i.e. 136/264) (the proportion receiving other subsequent treatments was weighted as per the resubmission's base case assumptions).

6.35 The steps of the analysis that contribute most to the final ICER are the extrapolation of outcomes to the model time horizon and the inclusion of all other resource utilisation costs.

6.36 The incremental costs were driven by the cost of first-line osimertinib, with cost offsets due to the cost of subsequent treatment (primarily later-line osimertinib treatment).

Table 13: Health care resource items: disaggregated summary of cost impacts

	Osimertinib	SC	Increment
First-line treatment	$[redacted]	$18,653	$[redacted]
• Excluding the additional rebate ($[redacted])	$[redacted]		$[redacted]
PF management	$2,950	$1,763	$1,187
AEs	$2,430	$5,925	–$3,495
Subsequent treatment	$2,382	$29,551	–$27,169
PD management	$2,221	$2,652	–$431
Palliative care	$12,993	$13,350	–$356
Mean total cost	**$[redacted]**	**$71,893**	**$[redacted]**
• Excluding the additional rebate ($[redacted])	**$[redacted]**		**$[redacted]**

Source: Constructed during the evaluation from Table 3.8.2, p145 of the resubmission and the 'Tagrisso (osimertinib) Economic Evaluation_July 2020 PBAC meeting.xlsm' workbook.

Note: Analyses were revised during the evaluation to reflect the cost of erlotinib only in the first-line treatment costs, 4 treatment cycles of carboplatin + gemcitabine, rather than 5.7; and reduced the proportion of patients that receive later-line osimertinib from 75.6% (i.e. 136/180) to 51.5% (136/264).

AE = adverse event; Osi = osimertinib; PD= progressive disease; PF = progression-free; SC = standard of care (erlotinib/gefitinib); Subs = subsequent.

6.37 The LYs and QALYs gained were accumulated primarily in the PF health state. The majority of the life years gained (70.5%) were accrued in the extrapolated period.

6.38 The results of the key sensitivity analyses for the revised base case, including and excluding the additional rebate ($[redacted]), are presented below.

Table 14: Results of key sensitivity analyses for the revised base case

	Including the additional rebate				Excluding the additional rebate			
	Inc. cost	Inc. QALYs	ICER	%	Inc. cost	Inc. QALYs	ICER	%
Revised base case	$[redacted]	[redacted]	$[redacted]	–	$[redacted]	[redacted]	$[redacted]	–
Proportion of patients expected to receive later-line osimertinib after discontinuation of 1L SC (base case: 51.5% (136/264))								
41.3% (109/264), based on FLAURA (#1)	$[redacted]	[redacted]	$[redacted]	14%	$[redacted]	[redacted]	$[redacted]	10%
First-line osimertinib utilisation (base case: capped at 20.7 packs)								
Based on extrapolated TTD, Gompertz – no utilisation cap (#2)	$[redacted]	[redacted]	$[redacted]	80%	$[redacted]	[redacted]	$[redacted]	67%
OS extrapolation time point (base case: 24 months)[a]								
Median OS (osi: 38.6 months, SC: 31.8 months) (#3)	$[redacted]	[redacted]	$[redacted]	8%	$[redacted]	[redacted]	$[redacted]	8%
Multivariate analyses								
#1 AND #2	$[redacted]	[redacted]	$[redacted]	94%	$[redacted]	[redacted]	$[redacted]	78%
#1 AND #3	$[redacted]	[redacted]	$[redacted]	24%	$[redacted]	[redacted]	$[redacted]	20%
#1, #2 AND #3	$[redacted]	[redacted]	$[redacted]	110	$[redacted]	[redacted]	$[redacted]	93%
#2 AND #3	$[redacted]	[redacted]	$[redacted]	95%	$[redacted]	[redacted]	$[redacted]	81%

Source: Constructed during the evaluation from the 'Tagrisso (osimertinib) Economic Evaluation_July 2020 PBAC meeting.xlsm' workbook.

[a] Convergence begins at time point of osimertinib extrapolation.

ICER = incremental cost-effectiveness ratio; OS = overall survival; osi = osimertinib; QALY = quality-adjusted life year; SC = standard of care (erlotinib/gefitinib); TTD = time to treatment discontinuation

The redacted table shows ICERs in the range of $15,000/QALY – $200,000/QALY when including the additional rebate; and $15,000/QALY - more than $200,000/QALY when excluding the additional rebate.

6.39 The ICER was most sensitive to the use of the extrapolated TTD curve to model the cost of first-line osimertinib.

6.40 Multivariate sensitivity analyses were conducted during the evaluation by changing the proportion costed as receiving later-line osimertinib to be consistent with that observed in the FLAURA trial, as well as estimating first-line utilisation of osimertinib based on the extrapolated TTD curve and setting the OS extrapolation time point to median OS. The ICER is highly sensitive to these cumulative changes.

6.41 The ESC advised that an appropriate respecified base case would (i) remove the rebate ($[redacted] per pack) [redacted]; (ii) assume [redacted] packs of osimertinib; (iii) apply cost-offsets of later line osimertinib in 51.5% of SC patients that discontinue treatment and (iv) extrapolate OS from median survival giving an ICER of more than $200,000/QALY gained. The ESC noted the ICER with the same assumptions but applying a cost of [redacted] packs of osimertinib (as proposed in the resubmission) was $105,000/QALY gained - $200,000/QALY gained. If the rebate was included, the values of these ICERs decreased to $105,000/QALY gained - $200,000/QALY gained and $75,000/QALY gained - $105,000/QALY gained, respectively. The sponsor increased the proposed rebate from $[redacted] to $[redacted] in the pre-PBAC response which resulted in a reduction in the ICER (assuming [redacted] packs of osimertinib) from $75,000/QALY - $105,000/QALY to $45,000/QALY - $75,000/QALY.

Drug cost/patient/course

6.42 The per patient drug costs for osimertinib and early-generation TKIs are presented in the table below. The cost for osimertinib per patient in the resubmission's economic evaluation was calculated to be $[redacted]. This is calculated by assuming [redacted] osimertinib packs dispensed per patient (based on the TTD curve in the FLAURA trial but capped when average use is [redacted] packs, to reflect the proposed RSA) and excluding the additional rebate [redacted]. Without the RSA (i.e. based on an uncapped TTD curve), the average number of packs used per patient would be [redacted], at a cost of $[redacted]. The drug cost for erlotinib/gefitinib in the economic evaluation was estimated to be $19,246 (revised to assume only the cost of erlotinib), using the TTD curve in FLAURA which has been extrapolated using parametric functions over the modelled time horizon.

Table 15: Drug cost per patient for osimertinib and SC

	Osimertinib			SC		
	Use in FLAURA	Model	Financial estimates	Use in FLAURA	Model	Financial estimates
Mean dose	80 mg/day	80 mg/day	80 mg/day	Erl: 150 mg/day Gef: 250 mg/day	Erl: 150 mg/day Gef: 250 mg/day	Erl: 150 mg/day Gef: 250 mg/day Afa: 40 mg/day
Mean duration	23.02 months truncated actual[a] mean (23.36 packs)	[redacted] months, cost capped at an average of [redacted] packs [b]	[redacted] months truncated actual[a] median ([redacted] packs)	14.42 months truncated actual[a] mean [c]	16.47 months (16.71 packs)	14.42 months truncated actual[a] mean [d]
Cost/patient/pack	$[redacted] [e]	$[redacted] [e]	$[redacted] [e]	$1,151.77 [f]	$1,151.77 [f]	$1,169.30 [g, h]
Cost/patient/course	$[redacted]	$[redacted]	$[redacted]	$16,851	$19,246	$16,975

Source: Constructed during the evaluation from the 'Tagrisso (osimertinib) Economic Evaluation_July 2020 PBAC meeting.xlsm' workbook and Section 4 of the resubmission.

Afa = afatinib; Erl = erlotinib; Gef = gefitinib; SC = standard of care

[a] Actual treatment duration accounts for dose interruptions. Durations are truncated as at the time of the latest data cut, some patients continued to receive randomised treatment (21.9% of patients randomised to osimertinib, and 4.7% of those randomised to SC).

[b] In the base case analysis, the number of osimertinib scripts was set up to (and including) an average of [redacted] packs, as accumulated by the time to treatment discontinuation curve. The average modelled was [redacted] packs.

[c] Estimated to be 14.63 packs of erlotinib or gefitinib

[d]. Estimated to be 14.63 packs of erlotinib or gefitinib, 15.68 packs of afatinib

[e] Cost excludes additional rebate [redacted]

[f] Revised to assume only the cost of erlotinib

[h] Weighted erlotinib:gefitinib:afatinib, 58.9%:28.4%:11.8%, and assuming an effective price for afatinib of $1,080.16

[i] Revised to update the DPMQ of gefitinib

Estimated PBS usage & financial implications

6.43 This resubmission was not considered by DUSC.

6.44 The resubmission has used a market share approach to estimate the financial impact of listing osimertinib in the first-line EGFRm NSCLC setting. An epidemiological approach was taken in the previous submission and the PBAC considered that patient numbers were overestimated (paragraph 7.14, Osimertinib PSD, July 2019 PBAC Meeting). The key data sources and parameter values used in the financial estimates are summarised below.

Table 16: Data sources and parameter values applied in the utilisation and financial estimates

Data	Value	Source	Comment
Eligible population			
No. patients who receive an EGFR-TKI for the first time, 2014−2018	2014: less than 10,000 2015: less than 10,000 2016: less than 10,000 2017: less than 10,000 2018: less than 10,000	PBS/RPBS service data, extracted from the DHS Pharmacy Claims Database on the 19 August 2019.	Only the 2017 observation was used in the analysis. While exclusion of the number of patients reported in 2014 has been reasonably justified (prior to the EGFRm listing in first-line), the exclusion of the other observations may not be. The ESC noted the actual number of patients treated with a TKI in 2019 should be available and requested that this be included in the ESC advice. Data provided subsequent to the ESC meeting indicated less than 10,000

Data	Value	Source	Comment
			patients received an EGFR-TKI for the first time in 2019[5].
Lung cancer incidence growth rate	3%	AIHW Cancer Incidence Projections (2012)	The average annual growth rate observed in updated AIHW lung cancer projections[6] was 2.16%.
Increase in EGFRm prevalence	2019: 1% 2020: 1%	An increase in the reported prevalence of EGFRm in Australian NSCLC patients (range: 17.9−26%)[7] relative to what the PBAC accepted at the time of listing erlotinib and gefitinib in the first-line setting (15%)	Given changes in the population demographic and limited availability of clinical trials in the setting of first-line NSCLC, the evaluation considered adjustment for these factors may be reasonable; however the estimates selected in the resubmission are not well supported and are highly uncertain.
Additional patients opting for PBS-subsidised treatment, due to lack of available clinical trials	2019: 5%	Assumption	
Number of grandfathered patients	Yr 1: less than 10,000	Assumption	This estimate has not been verified.
Treatment utilisation			
Uptake rate	Yr 1: 80% Yr 2+: 85%	Assumption	The maximum rate of uptake, 85%, was lower than in the previous submission (90% in Years 5 and 6 of listing). The resubmission stated that the rate of uptake assumed was consistent with other countries where osimertinib is reimbursed in the 1L setting. This could not be verified.
Market share of EGFR-TKIs	Erl: 58.9% Gef: 28.4% Afa: 11.8%	Services Australia PBS item statistics, Jan−Dec 2019 for EGFR-TKI items [a]	This is appropriate
Osimertinib (1L) scripts dispensed per patient	First year of treatment: [redacted] Second year of treatment: [redacted]	Median actual treatment duration of 20.7 months from the FLAURA trial, which equates to 21 scripts per patient. As this is a truncated estimate of treatment duration, a subsidisation cap is proposed based on an average of [redacted]	Whether the proposed average cost per patient would be realised, as intended through the RSA, relies on accurate estimates of patient numbers (paragraphs 7.11 and 7.13, Osimertinib PSD, July 2019 PBAC Meeting)

[5] Data extracted from the DHS Claims Database on the 17 June 2020

[6] AIHW. Lung cancer (C33-C34). Cancer data in Australia. Cat. no. CAN 122. Canberra: Australian Institute of Health and Welfare; 2019 [cited 2020 May]; Available from: https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/summary.

[7] DUSC review of TKI utilisation (Feb 2017), Stone E, Allen HA, Saghaie T, Abbott A, Daniel R, Mead RS, et al. High proportion of rare and compound epidermal growth factor receptor mutations in an Australian population of non-squamous non-small-cell lung cancer. Intern Med J. 2014 Dec;44(12a):1188-92 and IPSOS Market Research data ('180618 AZ NSCLC Report 2018 Q1 Final.pptx') presented in Attachment 7 of the resubmission.

Data	Value	Source	Comment
		packs per patient in the 1L setting	
Erlotinib/gefitinib scripts dispensed per patient	First year of treatment: 12.18 Second year of treatment: 2.45	Average treatment duration of 14.42 months (based on actual average treatment duration in FLAURA)	This is reasonable
Afatinib scripts dispensed per patient	First year of treatment: 12.18 Second year of treatment: 3.50	Average treatment duration of 14.42 months (based on actual average treatment duration in FLAURA)	While the total estimate of packs per patient is correct, there would be 13.05 scripts in the first year of treatment, and 2.63 in the second. Further, the resubmission has assumed 2.45 scripts per PBS patient in the second year of treatment (instead of 3.5).
No. patients who would have been treated with 2L osimertinib	Yr 1: less than 10,000 Yr 2: less than 10,000 Yr 3: less than 10,000 Yr 4: less than 10,000 Yr 5: less than 10,000 Yr 6: less than 10,000	PBAC osimertinib second-line submission (July 2018). The same assumptions were used to extrapolate the figures to 2026. Cost of 2L osimertinib use were offset in the proportion of patients expected to receive 1L osimertinib (i.e. 80−85%).	This represented 44-45% of patients who would have received 1L EGFR-TKI in the absence of 1L osimertinib. This estimate is lower than used in the economic analysis (51.5%).

Source: Table 4.1.1, p150 of the resubmission.
1L = first-line; 2L = second-line; EGFR-TKI = epidermal growth factor receptor tyrosine kinase inhibitor; EGFRm= epidermal growth factor receptor mutation positive; NSCLC = non-small cell lung cancer; RSA = risk-sharing arrangement.

6.45 The resubmission obtained PBS/RPBS data on the number of patients initiating treatment with a PBS-subsidised EGFR-TKI from 2014 to 2018. The number of eligible patients was extrapolated over the first six years of listing by applying a growth rate of 3% per annum to the number of patients initiating treatment in 2017. This annual growth rate was based on the AIHW lung cancer incidence projections published in 2012. The PBAC considered it was appropriate to apply an annual growth rate of 2.16% as recently published by the AIHW[8].

6.46 The ESC noted the financial model also included a growth rate (1%) due to increases in the prevalence of EGFRm and additional number of patients opting for PBS-subsidised treatment due to lack of trials (5% increase). The PBAC agreed with ESC that these rates were uncertain and considered application of these rates contributed to an increase in patient numbers that was not reasonable.

6.47 The ESC noted the actual number of patients treated with EGFR-TKIs in 2019 should be available and requested that this be included in the ESC advice. Data provided subsequent to the ESC meeting indicated less than 10,000 patients received an EGFR-TKI for the first time in 2019, which is lower than estimated in the financial model (less than 10,000).

[8] https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/contents/summary

6.48 The resubmission has assumed that of those eligible for a first-line EGFR-TKI, 80% in the first year of listing would opt to be treated with osimertinib, increasing to 85% in all subsequent years. While initial uptake was higher than in the previous submission (55%, increasing to 75% in Year 3) (and so is more consistent with the ESC consideration that that majority of eligible patients would receive osimertinib in this setting (paragraph 6.41, Osimertinib PSD July 2019 PBAC Meeting)), the maximum rate of uptake assumed (i.e. 85%) was lower than previously estimated (90% in Years 5 and 6). The sponsor revised the uptake of osimertinib in Year 3 to 6 to 90% in the pre-PBAC response, stating this was more aligned with the uptake observed in overseas markets.

6.49 The estimated number of osimertinib prescriptions dispensed per patient was based on the median actual treatment duration (20.7 months) reported in the FLAURA trial. As one osimertinib prescription supplies 30 days of therapy, this equates to [redacted] scripts[9] per patient ([redacted] in the first year of treatment, and [redacted] in the second year). The resubmission has proposed a subsidisation cap based on an average of [redacted] packs per patient.

6.50 The resubmission additionally considered that there would be less than 10,000 patients grandfathered onto PBS-subsidised treatment. This estimate was not justified in the resubmission. Grandfathered patients were each assumed to receive [redacted] scripts. The ESC considered the number of grandfathered patients may be overestimated and the use of [redacted] scripts to estimate the treatment cost for grandfathered patients may not be reasonable.

6.51 The numbers of prescriptions for erlotinib, gefitinib and afatinib were estimated based on the actual average treatment duration of SC in the FLAURA trial (14.42 months). Adjusting for the pack size for these agents, the average number of prescriptions dispensed per patient was estimated to be 14.63 for erlotinib and gefitinib (12.18 scripts in the first year of treatment, and 2.45 in the second) and 15.67 for afatinib (12.18[10] in the first year, and 3.50 in the second). Given that fewer than 5% of patients randomised to SC in FLAURA remained on treatment at the latest data cut, the use of these estimates was reasonable.

6.52 The reduction in the number of patients that would have received second-line osimertinib was based on estimates presented in the July 2018 submission for osimertinib in the later-line T790M M+ NSCLC setting. The same rate of first-line osimertinib uptake as applied in the resubmission (i.e. 80% in Year 1, increasing to 85% in subsequent years) was applied to estimate the number of patients in whom a reduction in second-line use of osimertinib is assumed.

6.53 The resubmission estimated the reduction in cost of second-line osimertinib by applying the average cost per patient of $[redacted] from the current (second-line)

[9] [redacted] packs is calculated based on [redacted] months = ([redacted] / 12) x (365.25 /30)

[10] While the total number of afatinib scripts per patient was correct, the number of scripts in the first year of treatment should have been 13.05, with 2.63 in the second year.

osimertinib RSA to the estimated number of patients who would no longer receive 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.

6.54 The resubmission proposed an additional rebate of $[redacted] for each estimated osimertinib prescription in the first-line setting. While it was proposed that the rebate arrangement is limited to a term of 5 years from the date of osimertinib PBS listing, the rebate was additionally estimated and applied in the sixth year estimates presented in the resubmission. This was corrected during the evaluation. The sponsor increased the proposed rebate to $[redacted] in the pre-PBAC response.

6.55 The estimated use of first-line osimertinib and associated financial impact are summarised below. The estimates presented include (a) correction to number of afatinib scripts per patient per year (paragraph 6.49) (b) amendment to gefitinib DPMQ to account for a reduction that occurred on 1 April 2020 and (c) removal of the rebate in Year 6 (paragraph 6.54).

Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. that uptake 1L osimertinib[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grandfathered patients	[redacted]					
No. patients that uptake 1L osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total 1L osimertinib scripts [b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of 1L osimertinib						
Cost to the PBS/RPBS, less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Substitution of first-line erlotinib, gefitinib and afatinib						
Erlotinib PBS/RPBS scripts [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gefitinib PBS/RPBS scripts [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Afatinib PBS/RPBS scripts [d]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Reduction in cost to the PBS/RPBS, less patient copayments [e]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Reduction in 2L osimertinib						
Patients eligible for 2L osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. patients with a reduction in 2L osimertinib use [a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
As a proportion of those who uptake 1L osimertinib	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Reduction in cost to the PBS/RPBS, less patient copayments [f]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the PBS/RPBS	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**	**$[redacted]**
Annual rebate [redacted]						
Estimated rebate ($[redacted] / [redacted]) [g]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
July 2019 PBAC consideration						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed [h]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net costs to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Table 4.1.5, p153, Table 4.2.1, p160; Table 4.2.2, p161, Table 4.2.4, p161, Table 4.3.1, p162; Table 4.3.2, p163; Table 4.3.5, p165, Table 4.3.3, p163; Table 4.3.4, p164; and Table 4.4.1, p167 of the resubmission, and Table 14, osimertinib, Public Summary Document, July 2019 PBAC meeting.

[a] Estimated uptake in 2021 is 80%, increasing to 85% in all subsequent years.

[b] [redacted] scripts in the first year of treatment, and [redacted] in the second year of treatment

[c] 12.18 scripts in the first year of treatment, 2.45 in the second year of treatment

[d] 13.04 scripts in the first year of treatment, and 2.63 in the second year of treatment (corrected from 12.18 scripts in first year of treatment, 2.45/ 3.5 in second year of treatment in PBS/ RPBS patients).

[e] In addition to the revision of the number of afatinib scripts, the cost per script of gefitinib was also updated to reflect the current price ($1,211.45)

[f] The cost of second-line osimertinib was estimated assuming a per-patient treatment course cost of $[redacted]. However patient copayments were estimated assuming [redacted] scripts per patient

[g] Revised to exclude the additional rebate in Year 6

[h] [redacted] scripts in the first year of treatment, [redacted] scripts in the second year of treatment

The redacted table shows that at Year 6, the estimated number of 1L osimertinib scripts was 10,000 – 50,000.

6.56 The total net cost to the PBS/RPBS of listing osimertinib was estimated to be approximately $30 - $60 million in Year 1, increasing to $30 - $60 million in Year 6, and a total of approximately more than $100 million in the first 6 years of listing, when the proposed annual rebate [redacted] was excluded. The total net cost to the PBS/RPBS of listing osimertinib including the proposed annual rebate was estimated to be approximately $20 - $30 million in Year 1 and a total of approximately more than $100 million in the first 6 years of listing. This is compared with the total net cost to the PBS over 6 years being more than $100 million, as presented in the previous submission.

6.57 The PBAC considered the estimated number of eligible patients should be revised as follows:

- Apply a lung cancer incident growth rate of 2.16% (paragraph 6.45);
- Remove the additional 1% and 5% growth in patient numbers (paragraph 6.46);
- Use actual patient numbers treated with first-line TKIs in 2019 in the financial model (645) (paragraph 6.47);
- Apply an uptake of first-line osimertinib of 90% in Year 3 to 6 as proposed by the sponsor in the pre-PBAC response (paragraph 6.48); and
- Apply the revised first-line uptake (90% in Year 3 to 6) to the number of patients in whom a reduction in second-line use of osimertinib is assumed (paragraph 6.52).

The revised number of patients treated first-line with osimertinib and the financial implications applying these assumptions (and assuming [redacted] packs per patient) are summarised in the table below. The estimated impact of the rebate proposed in the pre-PBAC response ($[redacted]) is also presented.

Table 18: Revised estimated use and financial implications of first-line osimertinib

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Eligible patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. that uptake 1L osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Grandfathered patients	[redacted]					
No. patients that uptake 1L osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total 1L osimertinib scripts	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of 1L osimertinib						
Cost to the PBS/RPBS, less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Substitution of first-line erlotinib, gefitinib and afatinib						
Reduction in cost to the PBS/RPBS, less patient copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Reduction in 2L osimertinib						
Patients eligible for 2L osimertinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
No. patients with a reduction in 2L osimertinib use	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
As a proportion of those who uptake 1L osimertinib	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
Reduction in cost to the PBS/RPBS, less patient copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Annual rebate [redacted]						
Estimated rebate ($[redacted] / [redacted]) per script	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net cost to the PBS/ RPBS including rebate	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

The redacted table shows that at Year 6, the estimated number of 1L osimertinib scripts was 10,000 – 50,000.

6.58 The PBAC noted the revised total net cost to the PBS/RPBS of listing osimertinib was estimated to be approximately $20 - $30 million in Year 1, increasing to $30 - $60 million in Year 6, and a total of approximately more than $100 million in the first 6 years of listing, when the proposed annual [redacted] was excluded. Including the revised proposed rebate, the estimated total net cost to the PBS/ RPBS was more than $100 million in the first 6 years of listing.

Financial Management – Risk Sharing Arrangements

6.59 In addition to the proposed SPA, the resubmission proposed two forms of RSAs. The first was in the form of a subsidisation cap and the agreed expenditure caps for first-line osimertinib treatment, accounting for cost savings resulting from reduced utilisation of osimertinib as second-line treatment, would be added to the current osimertinib subsidisation caps to form one set of annual subsidisation caps for

osimertinib treatment of EGFRm NSCLC. The resubmission proposed that [redacted]% of expenditure exceeding the subsidisation caps is rebated by the sponsor.

6.60 The PBAC noted the lower treatment cost per patient applied in the economic and financial modelling (paragraph 6.26) was proposed to be achieved through a RSA in which the financial caps are calculated as the cost per patient multiplied by the number of patients.

6.61 The current expenditure caps for second-line osimertinib are summarised in Table 19.

Table 19: Expenditure cap and Commonwealth expenditure for second-line osimertinib

	Year 1 (Feb 2019 to Jan 2020)	Year 2 (Feb 2020 to Jan 2020)	Year 3 (Feb 2021 to Jan 2022)	Year 4 (Feb 2022 to Jan 2023)	Year 5 (Feb 2023 to Jan 2024)
Expenditure cap	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Commonwealth expenditure	$[redacted]	-	-	-	-

6.62 The estimated net expenditure on first-line osimertinib applying the changes to the patient estimates outlined in paragraph 6.57 is summarised in Table 20.

Table 20: Estimated net expenditure on osimertinib if the first-line indication is listed on the PBS, using revised patient numbers as specified in paragraph 6.57

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Cost of 1L osimertinib	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Reduction in cost of 2L osimertinib	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net expenditure on osimertinib	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

6.63 The second form of RSA proposed was an additional rebate delivered via an annual rebate, paid quarterly, [redacted]. The resubmission proposed that this rebate arrangement would be limited to a term for 5 years from the date of osimertinib PBS listing.

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

7 PBAC Outcome

7.1 The PBAC recommended the listing of osimertinib for the first-line treatment of locally advanced or metastatic (Stage IIIB or IV), epidermal growth factor receptor mutation positive (EGFRm), non-small cell lung cancer (NSCLC). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of osimertinib would be acceptable if the incremental cost effectiveness ratio was less than $45,000/QALY – $75,000/QALY gained.

7.2 The PBAC is satisfied that osimertinib provides, for some patients, a significant improvement in efficacy and reduction in toxicity over PBS listed EGFR-TKIs. The PBAC recalled that it had previously considered the claim that osimertinib is superior to EGFR-TKIs for PFS and safety was reasonable. However, it previously considered the

claim of superiority based on OS was not reasonable as the incremental benefit was uncertain due to immaturity of the data and potentially overestimated due to the likely underuse of second-line osimertinib post-progression in the comparator arm (paragraph 6.24, Osimertinib PSD, July 2019 PBAC meeting). The PBAC considered the data provided in the resubmission, based on a longer duration of follow up and with a higher proportion of patients in the comparator arm receiving second-line osimertinib, supported the claim of superiority for OS.

7.3 The PBAC considered separate restriction criteria for first-line and second-line use of osimertinib were reasonable (paragraph 3.3). The PBAC considered the restriction criteria in paragraph 3.1, including the changes proposed by the Secretariat, were appropriate. The PBAC recommended that the first-line grandfather listing could be removed after 12 months and the second-line grandfather listing could be removed immediately as it was over 12 months old. The PBAC considered it would be appropriate to amend the second-line osimertinib listing to be Authority Required (telephone/online) for initial treatment and Authority Required (Streamlined) for continuing treatment.

7.4 The PBAC noted the key evidence to support the clinical claim (the FLAURA trial) remained unchanged from the previous submission but included OS data based on a longer duration of follow up (35.8 months compared to 18.6 months in the previous submission). The PBAC noted the OS hazard ratio was 0.799 (95%CI: 0.640, 0.996) with a difference in median OS of 6.8 months.

7.5 The PBAC considered the respecified economic model applying a cost of [redacted] packs of osimertinib, as outlined in paragraph 6.41, provided a reasonable basis for assessing the cost effectiveness of osimertinib. The PBAC noted the ICER was $105,000/QALY - $200,000/ QALY gained excluding the proposed rebate [redacted]. The PBAC recalled it had previously considered osimertinib would be cost effective in this treatment setting if the ICER was no more than $45,000/QALY - $75,000/QALY gained (paragraph 7.13, Osimertinib PSD, July 2019 PBAC meeting). The PBAC noted the pre-PBAC response proposed an ICER of $45,000/QALY - $75,000/QALY (paragraph 6.41). The PBAC considered the respecified economic model incorporating clinical data with a longer duration of follow up and evidence of an OS benefit, provided a more reliable estimate of cost effectiveness and advised a higher ICER threshold was reasonable in this circumstance. The PBAC considered that osimertinib would be cost effective for the first-line treatment of EGFRm NSCLC if the ICER was less than $45,000/QALY - $75,000/QALY gained.

7.6 The PBAC considered that to achieve an ICER of less than $45,000/QALY - $75,000/QALY the cost of osimertinib for first-line treatment of EGFRm NSCLC would need to be reduced by approximately $[redacted], which was consistent with the revised rebate ($[redacted]) [redacted] offered in the sponsor's pre-PBAC response. The PBAC noted that while the specific administration of rebates is a matter for Government, for osimertinib to be cost effective, the cost per patient which results in an ICER of below $45,000/QALY - $75,000/QALY would need to be realised in a way

which provided certainty that it is achieved in practice and will continue to be achieved in all future years of PBS listing.

7.7 The PBAC noted the economic and financial modelling applied a lower treatment cost per patient (based on ~[redacted] packs) compared to the treatment cost estimated using the time to treatment discontinuation modelling (based on ~[redacted] packs) (paragraph 6.26). The PBAC noted the lower treatment cost was proposed to be achieved through a RSA (paragraph 6.60). The PBAC recalled it had previously considered achieving a lower treatment cost per patient is dependent on meeting (or exceeding) the utilisation estimates that are used to calculate the subsidisation caps for the RSA (paragraph 7.11, Osimertinib PSD, July 2019 PBAC Meeting).

7.8 The PBAC noted the estimated number of patients expected to be treated with first-line osimertinib was based on the number of patients currently treated in the first-line setting with EGFR-TKIs. The PBAC considered the market share approach used in the resubmission was more appropriate than the epidemiological approach used in the July 2019 submission and provided more certainty regarding the utilisation and hence financial estimates. The PBAC considered the estimated number of patients treated with first-line osimertinib, and the reduced use of second-line osimertinib, should be amended as outlined in paragraph 6.57.

7.9 The PBAC noted the significant number of grandfathered patients (less than 10,000) included in the financial estimates at a cost of [redacted] packs (compared to [redacted] packs for incident patients). The PBAC also noted the financial estimates assumed all incident patients in Year 1 receive a full year of treatment ([redacted] packs) which will overestimate the cost as patients will commence treatment throughout the year and, on average, will receive a lower number of packs. The PBAC advised a lower uptake rate should be applied in Year 1 to account for a lower number of prescriptions per patient.

7.10 The PBAC considered a RSA for osimertinib would be required with subsidisation caps accounting for expenditure on first-line osimertinib and cost savings resulting from reduced utilisation of second-line osimertinib. The PBAC considered a [redacted]% rebate payable for Commonwealth expenditure over the caps was appropriate.

7.11 The PBAC noted that supportive advice from the Medical Services Advisory Committee was foreshadowed to include osimertinib on the existing MBS Item 73337 for the purpose of assessing PBS eligibility for treatment, and that this amendment to the MBS listing would be required alongside the recommended PBS listing.

7.12 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for osimertinib:

a) Treatment with osimertinib is expected to provide a substantial and clinically relevant improvement in efficacy and reduction in toxicity over alternative therapies;

b) Treatment with osimertinib is not expected to address a high and urgent unmet clinical need because other subsidised therapies (including osimertinib in the second-line setting) are available;
c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.13 The PBAC noted that this submission is not eligible for an Independent Review as it was recommended for listing.

Outcome:
Recommended.

8 Recommended listing

8.1 Add new first-line treatment listing at the same time MBS item 73337 is updated, as follows:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
OSIMERTINIB osimertinib 80 mg tablet, 30	11622Q	1	30	5	Tagrisso

Initial first-line Restriction Summary [NEW] / ToC: [New]:

Concept Id: (for internal Dept. use)	**Category / Program:** Section 85 – General Schedule – Code (GE)
	Prescriber type: ☒ Medical Practitioners
	Restriction Type / Method: ☒Authority Required – immediate/real time assessment by Services Australia (telephone/online/emergency)
9828	**PBS indication***:* Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
	Treatment phase: Initial treatment as first-line epidermal growth factor receptor tyrosine kinase inhibitor therapy
7890	**Clinical criteria:**
7889	The treatment must be the sole PBS-subsidised therapy for this condition
	AND
7601	Patient must have a WHO performance status of 2 or less
	AND
14392	Patient must not have previously received PBS-subsidised treatment with this drug for this condition
	AND
9831	Patient must not have received previous PBS-subsidised treatment with another epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI); OR
9832	Patient must have developed intolerance to another epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal
9836	**Population criteria:**
Edit 9835 (flow-on change to all)	Patient must have evidence in tumour material of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors
25796	**Administrative Advice:** Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised
7608	**Administrative Advice:** Special Pricing Arrangements apply

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
OSIMERTINIB osimertinib 40 mg tablet, 30	11620N	1	30	5	Tagrisso
osimertinib 80 mg tablet, 30	11622Q	1	30	5	Tagrisso

Continuing first-line Restriction Summary [NEW / 8530 with treatment phase edited] / ToC: [NEW / 8537]:

Category / Program: Section 85 – General Schedule – Code GE
Prescriber type: ☒ Medical Practitioners
☒ Authority Required – Streamlined [new code]
PBS indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase: Continuing treatment of first-line EGFR tyrosine kinase inhibitor therapy
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
Administrative advice: No increase in the maximum number of repeats may be authorised
Administrative advice: Special Pricing Arrangements apply

First-line Grandfather treatment Restriction Summary [NEW] / ToC: [NEW]:

Category / Program: Section 85 – General Schedule – Code GE
Prescriber type: ☒ Medical Practitioners
☒Authority Required – immediate/real time assessment by Services Australia (telephone/online)
PBS indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase: Transitioning from non-PBS to PBS-subsidised supply as first-line EGFR tyrosine kinase inhibitor therapy – 'Grandfather' treatment
Clinical criteria:
Patient must have received non-PBS subsidised treatment with this drug as first-line EGFR tyrosine kinase inhibitor therapy for this PBS indication 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 evidence in tumour material of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors that was obtained prior to initiating non-PBS subsidised treatment
Prescribing instructions: A Grandfathered 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: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333
Administrative advice: No increase in the maximum quantity or number of units may be authorised
Administrative advice: No increase in the maximum number of repeats may be authorised
Administrative advice: Special Pricing Arrangements apply
Administrative advice: This grandfather restriction will cease to operate from 12 months after the date specified in the Clinical criteria

Flow-on changes:

Amend osimertinib's existing second-line treatment listings as follows:

- Edit Treatment phase descriptions to make first-line and second-line treatment quickly distinguishable:

Treatment Phase: Continuing treatment of second-line EGFR tyrosine kinase inhibitor therapy
Treatment Phase: Initial treatment as second-line EGFR tyrosine kinase inhibitor therapy
Treatment Phase: Continuing treatment of second-line EGFR tyrosine kinase inhibitor therapy

- Add a clinical criterion into the Initial treatment restriction to prevent re-treatment with osimertinib if the patient has taken it in first-line treatment:

To PBS item code: 11622Q/Restriction Summary 8527:

Clinical criteria:
Patient must not have previously received this drug for this condition.

- Amend Authority approval method from 'written-only' where it appears (Initial/Grandfather) to 'telephone/online';
- Remove 'Complex Authority Required' flag and replace associated administrative note with that applying to a telephone/online authority approval listing (concept Id 25796);
- Amend Authority approval method from 'telephone/online' where it appears (Continuing) to 'Streamlined'; and
- Remove Grandfather listing that is now more than 12 months old.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

The sponsor had no comment.