TAR 491 – Osimertinib for non-small cell lung cancer with EGFR mutations, first- and second-line treatment

Date	19 April 2023
Level of Analysis	Standard

This assessment provides an estimate of the likely cost-effectiveness range of Osimertinib for metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor mutations (EGFRm), and its budgetary impact, in the first- and second-line setting.

A summary of the proposal is provided in the table below.

PROPOSAL OVERVIEW
Pharmaceutical Osimertinib (TAGRISSO) 40 mg and 80 mg tablets
Supplier AstraZeneca New Zealand
Proposed Indication First-line treatment for people with metastatic EGFRm non-small cell lung cancer Second-line treatment for people with metastatic EGFRm non-small cell lung cancer and T790M mutations
Dosing 80 mg daily
Pharmaceutical Price Net S 9(2)(b) (gross S 9(2)(b)) per pack of 30 x 40mg tablets (Dec 2019 proposed S 9(2) terms - A1355981) Net S 9(2)(b) (gross S 9(2)(b)) per pack of 30 x 80mg tablets (Dec 2019 proposed S 9(2) terms - A1355981)
Application First-line: AstraZeneca New Zealand, December 2019 Second-line: AstraZeneca New Zealand, November 2017
PTAC PRIORITY **First-line** PTAC (August 2020): Cost-neutral CaTSoP (April 2021) (now CTAC): High **Second-line** CaTSoP (April 2018): Deferred PTAC (August 2020): Deferred CaTSoP (April 2021): High
PHARMCONNECT REFERENCE First-line: P-001526 Second-line: P-00329

Executive Summary

An application for the funding of osimertinib for metastatic EGFRm positive NSCLC in the first-line (1L) setting was received from AstraZeneca in December 2019 (A1356031). An application for funding osimertinib in the second-line (2L) setting was received in November 2017 (A1091040).

EGFRm positive NSCLC is a type of lung cancer found in about 20% of NSCLC cases. The most common symptoms experienced by people with metastatic lung cancer are fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. As the disease advances, health related quality of life (HRQoL) substantially deteriorates. Current treatment options include first generation Tyrosine Kinase Inhibitors (TKIs) erlotinib and gefitinib while subsequent treatment lines include platinum-based chemotherapy (2L) and docetaxel (3L).

Review of Cost-Utility Analyses

In the 2017 application for 2L, the supplier submitted a cost utility analysis (CUA) (A1091099) which estimates that osimertinib is cost-saving. However, in the model report (A1091100), the cost-effectiveness is claimed to be S 9(2)(b)(ii), 9(2)(ba) per QALY. This roughly translates to S 9(2)(b)(ii), 9(2)(ba)(i) & per QALY or S 9(2) QALYs per $1 million invested. However, results may be misleading given:

- Use of immature overall survival data from phase II trials
- The model submitted is a global model, calibrated to the United Kingdom context, so aspects of the treatment paradigm and resource use are misleading
- The model type was partitioned survival, which is often appropriate for oncology treatments, however a Markov model was considered preferable given its greater flexibility.

No CUA was provided in the 1L application. Pharmac have therefore built two CUA models to estimate the cost-effectiveness of osimertinib for EGFRm positive NSCLC, in both the 1L and 2L settings.

Pharmac have therefore built two CUAs to estimate the cost-effectiveness of osimertinib for EGFRm positive NSCLC, in both the 1L and 2L settings.

Methods of international CUAs from the National Institute for Health and Care Evidence (NICE), the Pharmaceutical Benefits Advisory Committee (PBAC) and the Canadian Agency for Drugs and Health Technology (CADTH) have all been published, however the results of these are confidential.

Summary of Pharmac Cost-Utility Analysis

A CUA was undertaken by Pharmac staff to estimate the cost-effectiveness of osimertinib for metastatic EGFRm positive NSCLC. The economic model used data derived from the FLAURA (1L) and AURA3 (2L) trials which indicated longer overall survival (OS) and progression-free survival (PFS) for people receiving osimertinib.

In the 1L setting, the cost utility of osimertinib compared to current treatments for metastatic EGFRm positive NSCLC is estimated to be in the range of S 9(2)(b)(ii), 9 QALYs gained per $1 million invested. The results of the CUA were generally not sensitive to changes in model parameters

due to the high cost of osimertinib relative to comparator treatments. The results indicate that, at the time of writing and in this population, the cost-effectiveness of osimertinib is [redacted].

In the 2L setting, the cost utility of osimertinib compared to current treatments for metastatic EGFRm positive NSCLC is estimated to be in the range of [redacted] QALYs gained per $1 million invested. The results of the CUA were generally not sensitive to changes in model parameters due to the high cost of osimertinib relative to comparator treatments. The results indicate that, at the time of writing and in this population, the cost-effectiveness of osimertinib is [redacted].

Summary of Budget Impact Analysis

If funded in a 1L setting, the number of people starting treatment was estimated to be 116 in year 1, increasing to 121 in year 5. If funded in a 2L setting, the number of people starting treatment was estimated to be 76 in year 1 and falling to 41 in year 5.

The net cost to the Combined Pharmaceutical Budget (CPB) of funding osimertinib at 1L is expected to be [redacted] in year 1 with a five-year net present value (NPV) of [redacted]. Funding Osimertinib at 2L is expected to cost the CPB [redacted] in year 1, with a five-year NPV of [redacted].

The net cost to the wider health system of funding osimertinib 1L is expected to be [redacted] in year 1 with a five-year NPV of [redacted]. The difference in cost to the wider health system compared with the pharmaceutical budget is predominantly driven by the pharmacy margin on osimertinib sales, which is significant given its high list price.

The net cost to the wider health system of funding osimertinib 2L is expected to be [redacted] in year 1 with a five-year NPV of [redacted]. The difference in cost to the wider health system compared with the pharmaceutical is predominantly driven by the pharmacy margin on osimertinib sales and the cost of additional T790M mutation tests.

1. Proposal Overview

2.1 Disease description

The disease description below is an edited and abridged version of the disease description in the August 2020 PTAC paper (A1366184).

Non-Small Cell Lung Cancer (NSCLC)

Lung cancer can be broadly categorised into two main types: small cell lung cancer and NSCLC. NSCLC is the most common type of lung cancer. NSCLC can be sub-classified as squamous or non-squamous (including adenocarcinoma or large cell histology) histological types. The majority of people with NSCLC present with advanced stage IIIB (locally advanced) or IV (metastatic) disease at diagnosis (Health Quality and Safety Commission NZ; 2016). A large proportion of those diagnosed with early-stage disease eventually experience disease recurrence following treatment and progress to advanced/metastatic disease.

Survival from lung cancer in New Zealand is poor with a five-year survival of 9.5% for men and 11% for women. Early-stage lung cancer is often asymptomatic, so the majority of patients are diagnosed at a late stage. The most common symptoms experienced by people with advanced lung cancer are fatigue, loss of appetite, shortness of breath, cough, pain, and blood in sputum. As the disease advances, HRQoL substantially deteriorates (Wood et al. Qual Life Res. 2019;28:1849-1861).

Epidermal Growth Factor Receptor mutation (EGFRm)

In a subset of NSCLC cases, tumours are EGFRm positive. Epidermal growth factor receptor tyrosine kinase is the cell-surface receptor for members of the epidermal growth factor family of extracellular protein ligands. Mutations that lead to EGFR overexpression or overactivity have been associated with a number of cancers, including lung cancer. Specific activating mutations in the tyrosine kinase domain of the EGFR (exon 19 deletions, L858R point mutation in exon 21) are associated with increased responsiveness to EGFR TKIs in lung cancer.

In New Zealand, 21.6% of people with NSCLC tested for EGFRm have EGFRm positive tumours (Tin Tin et al. Cancer Epidemiol. 2018;57:24-32). There is a higher tested and reported incidence of EGFR mutation in people of south-east Asian ethnicity (39.6%) and Pacific ethnicity (24.4%) than in people of New Zealand European (17.6%) or Māori (10.2%) ethnicity (McKeage et al. 2015. Technical report for the Heath Innovation Partnership of the Health Research Council of New Zealand and National Health Committee).

People treated with EGFR TKIs generally develop resistance, the most common of which is T790M mutation. This mutation causes the efficacy of first generation TKIs to wane, however osimertinib has been shown to be effective among people who have developed the T790M mutation.

Proposal Framework

Table 1 below provides a summary of the patient population; intervention; comparator treatment; and main outcomes of treatment (PICO) of osimertinib for NSCLC EGFRm if it were funded in the 1L setting.

Table 2 summarises the PICO for osimertinib if it were funded in the 2L setting.

Table 1. PICO (1L treatment)

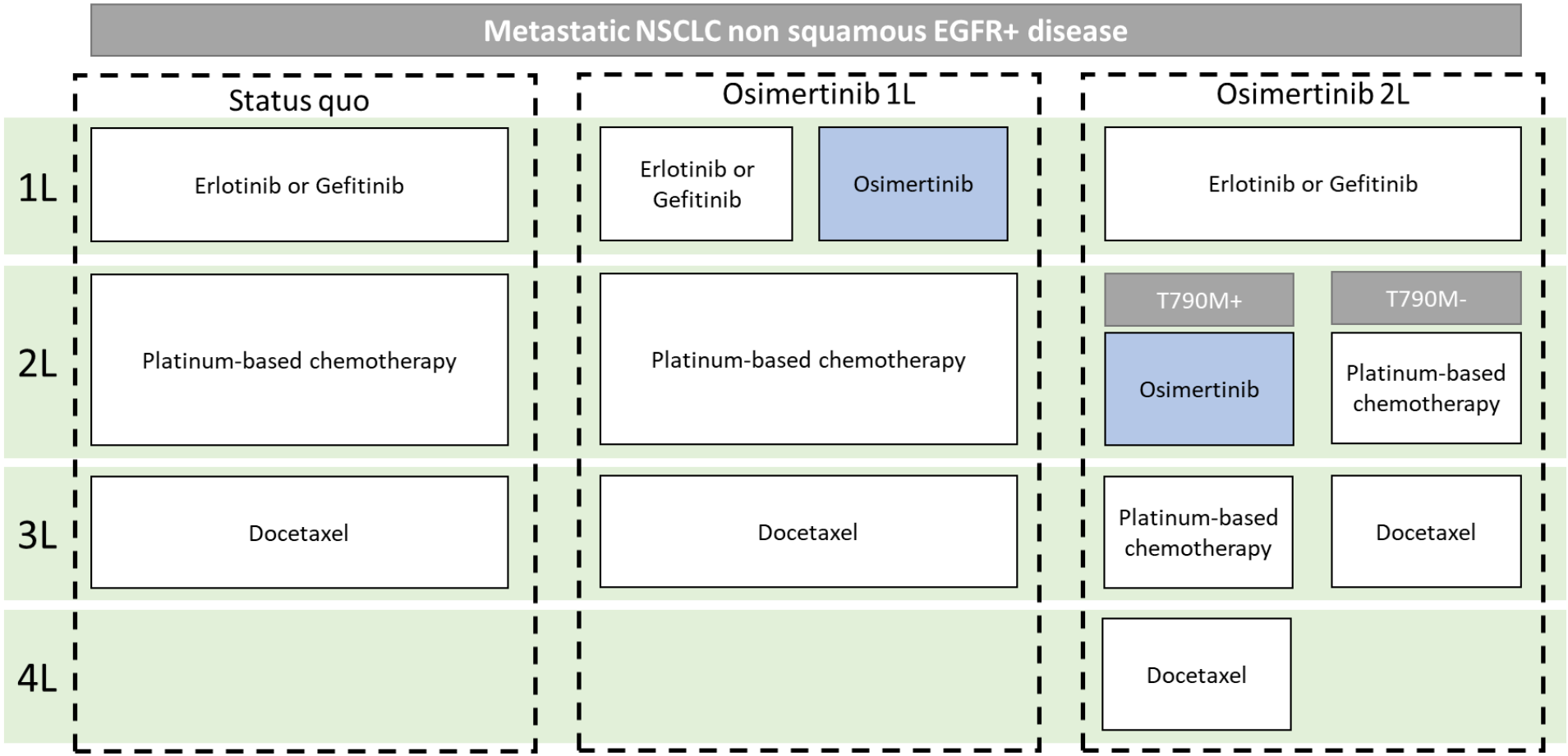
PICO	
POPULATION	Patients with locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous NSCLC, who have the EGFR tyrosine kinase mutation, and who are either • Treatment naïve or • Have discontinued gefitinib or erlotinib due to intolerance and do not have progressed disease
INTERVENTION	One osimertinib 80 mg tablet per day until disease progression or unacceptable toxicity. Followed by subsequent treatment with, in order: 1. Platinum-based chemotherapy until disease progression 2. Docetaxel (75mg/m^2 3 weekly, 90 min infusion) until disease progression All therapies taken until disease progression, unacceptable toxicity or death
COMPARATOR	For treatment naïve patients: erlotinib, one 150 mg tablet daily or gefitinib, one 250 mg tablet daily, until disease progression or unacceptable toxicity Followed by subsequent treatment with, in order: 1. Platinum-based chemotherapy 2. Docetaxel (75mg/m^2 3 weekly, 90 min infusion) All therapies taken until disease progression, unacceptable toxicity or death
OUTCOME	Longer PFS and OS as reported in the FLAURA trial (see Table 3)

Table 2: PICO (2L treatment)

PICO	
POPULATION	Patients with Stage IIIb or IV, non-squamous NSCLC, who have the EGFR tyrosine kinase mutation with T790M mutation and have progressed following 1L treatment with a TKI.
INTERVENTION	One osimertinib 80 mg tablet per day until disease progression or unacceptable toxicity. Followed by subsequent treatment with, in order: 1. Platinum-based chemotherapy 2. Docetaxel (75mg/m^2 3 weekly, 90 min infusion) All therapies taken until disease progression, unacceptable toxicity or death.
COMPARISON	Platinum-based chemotherapy taken until disease progression, unacceptable toxicity or death. Upon progression, subsequent treatment with docetaxel (75mg/m^2 3 weekly, 90 min infusion) taken until progression, unacceptable toxicity or death
OUTCOME	Longer PFS and OS as reported in the AURA3 trial (see Table 4)

The treatment paradigm of each proposal as well as the status quo is also illustrated in Figure 1 on the following page.

Figure 1: Treatment paradigm



2. Health Benefits

2.2 Clinical Evidence

The key evidence used to inform this assessment is summarised in Table 3 (1L) and Table 4 (2L) below.

Table 3: Key evidence for the 1L use of osimertinib

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
FLAURA	Phase III, double-blind, 1:1 randomised control trial	Patients had locally advanced or metastatic NSCLC, had not previously received treatment for advanced disease, and were eligible to receive first-line treatment with gefitinib or erlotinib. Confirmation of the EGFR exon 19 deletion (Ex19del) or p.Leu858Arg (L858R) EGFR mutation, alone or co-	n=556 Osimertinib, n= 279 Comparator, n=277 (gefitinib n=183; erlotinib n=94)	Oral osimertinib (80 mg once daily). Or oral gefitinib (250 mg once daily) or erlotinib (150 mg once daily). Randomised treatment was continued until progression, unacceptable toxicity or withdrawal of patient consent.	The median duration of PFS follow up: 15.0 months for osimertinib and 9.7 months for the comparator	Primary end point: duration of PFS according to RECIST, version 1.1. PFS: time from randomisation until objective disease progression. Median treatment exposure: 16.2 month for osimertinib and 11.5 months for comparator. • Median PFS: Osimertinib 18.9 months (95% CI=15.2-21.4); comparator group 10.2 months (95% CI=9.6-11.1). • HR for disease progression or death, 0.46; 95% CI=0.37-0.57; p<0.001. • At 18 months, the survival for the osimertinib group was 83% (95% CI=78-87) compared to 71% (95% CI=65-76) in the comparator group.	• Overall AEs (any grade) were the same between groups (98%). • Rash or acne, diarrhoea and dry skin were the three most common AEs in both groups. • AEs of grade 3 or higher were reported in fewer patients in the osimertinib group than in the comparator group (34% vs. 45%).	Soria et al. N Engl J Med. 2018;372:113-125

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
		occurring with other EGFR mutations. Median age, 64 years.						
FLAURA	FLAURA trial, as described above.	FLAURA trial population, as described above.	FLAURA trial population, as described above.	FLAURA trial intervention, as described above.	The median duration for follow up for OS: 35.8 months for osimertinib and 27.0 months for the comparator group.	OS was a secondary outcome of the FLAURA trial. Median treatment exposure: 20.7 months for osimertinib and 11.5 months for the comparator. • The median OS was 38.6 months (95% CI=34.5-41.8) in the osimertinib group and 31.8 months (95% CI=26.6-36.0) in the comparator group (HR for death, 0.80; 95.05% CI=0.64-1.00; p=0.046). • 48% (n=133) of osimertinib patients and 65% (n=180) of comparator group progressed to a first subsequent therapy. 26% (n=72) of osimertinib and 33% (n=92) of comparator group received a second subsequent therapy. No statistical analysis was reported for the subsequent therapy lines. • PFS at 18 months among patients with CNS metastases was 58% (95% CI=40-72) in the osimertinib group and 40% (95% CI=25-55) in the comparator group (HR for disease progression or death, 0.48; 95% CI=0.26-0.86).	• Adverse events of grade 3 or higher were reported in 42% of the patients in the osimertinib group and in 47% of those in the comparator group. • Dose interruption, dose reduction and permanent discontinuation were similar between the two groups. • At 36 months, no new safety signals were observed. AEs of grade 3 or higher and rates of treatment discontinuation due to AEs were similar in the two groups, despite the longer duration of exposure to osimertinib.	Ramalingam et al. N Engl J Med. 2020;382:41-50

Table 4: Key evidence for the 2L use of osimertinib

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety (if reported)	Citation
AURA3	Phase III, open label, randomised (2:1) study	Patients with locally advanced or metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and whose tumours harbour a T790M mutation within the EGFR gene (T790M tested during screening with cobas EGFR Mutation Test (tumour tissue biopsy samples); confirmed centrally in plasma circulating tumour DNA on the cobas® EGFR Mutation Test v2; Roche Molecular Systems Inc).	N = 419 (osimertinib N=279, Platinum-pemetrexed N=140)	80 mg osimertinib orally (once daily) OR intravenous pemetrexed 500 mg/m^2 of body surface area plus either carboplatin (target area under the curve, 5) or 75 mg/m^2 cisplatin every 3 weeks for up to six cycles	Median PFS follow up was 8.3 months	The primary efficacy end point was the duration of investigator-assessed PFS according to RECIST v1.1; Secondary objectives included: response rate per investigator assessment, response duration, disease control rate, tumour shrinkage, OS, patient-reported outcomes, and safety and side-effect profiles. Predefined subgroup analyses included the duration of PFS and response rate among patients for whom EGFR T790M status was determined by means of a plasma ctDNA test and among those with CNS metastases. • The median duration of progression-free survival was significantly longer with osimertinib than with platinum therapy plus pemetrexed (10.1 months vs. 4.4 months; hazard ratio; 0.30; 95% confidence interval [CI], 0.23 to 0.41; P<0.001)	The proportion of patients with adverse events of grade 3 or higher was lower with osimertinib (23%) than with platinum therapy plus pemetrexed (47%)	Mok et al. N Engl J Med. 2017;376:629-40

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety (if reported)	Citation
AURA3	AURA3 trial, as described above.	AURA3 trial population, as described above.	AURA3 trial population, as described above.	AURA3 trial intervention, as described above.	Treatment until investigator-assessed disease progression per RECIST v1.1 Cross over to osimertinib permitted at progression	Data cut-off 15 March 2019. 188 (67%) osimertinib and 93 (66%) platinum-pemetrexed patients had died. First subsequent treatment: osimertinib in N=98 (86%) post platinum-pemetrexed, median 11.0 (range 0.1 to 44.0) months exposure. Post-osimertinib pemetrexed N=109 (66%). <u>OS secondary endpoint:</u> Median OS 26.8 months osimertinib vs 22.5 months platinum-pemetrexed (HR 0.87 (95% CI: 0.67 to 1.12; 95.564% CI: 0.67 to 1.13, P=0.277). Exploratory crossover-adjusted (RPSFTM* on treatment method) median OS 26.8 months osimertinib vs 15.9 months platinum-pemetrexed (HR 0.54, 95% CI: 0.18 to 1.60). Subgroup OS: nonsignificant higher risk of death with osimertinib in male patients and patients with CNS metastases at baseline. Numerically longer median OS with negative (vs positive) baseline T290M status.	Related adverse events (AEs) in 237 (85%) osimertinib vs 121 (89%) platinum-pemetrexed; grade ≥3 AEs in 24 (9%) and 46 (34%), respectively. Discontinuations: 4 (5%) osimertinib vs 12 (9%) platinum-pemetrexed. Interstitial lung disease (N=4) and pneumonitis (N=7; 2 fatal) possibly related to osimetinib; 1 case each with platinum-pemetrexed. Deaths due to AEs pre-crossover: 12 (4%) osimetinib vs 2 (1%) platinum-pemetrexed. After crossover: 1 of 5 fatal AEs due to respiratory failure, possibly related. QOL not reported.	Papadimitrakopoulou et al. Ann Oncol. 2020;31:1536-44

RECIST – Response Evaluation Criteria in Solid Tumours, HR – Hazard Ratio, AE – Adverse Event, CI – Confidence Interval, CNS – Central Nervous System, RPSFTM – Rank-Preserving Structural Failure Time Models, QOL – Quality of Life

2.2 Review of Clinical Evidence

The proposals have been reviewed by both the Pharmacology and Therapeutics Advisory Committee (PTAC) and the Cancer Treatments Subcommittee of PTAC (CaTSoP, now the Cancer Treatments Advisory Committee - CTAC). A summary of the clinical advice and recommendations provided by the committees is provided in Table 5.

Table 5. Clinical Advice Summary

Committee	Proposal	Recommendation
CaTSoP April 2018 (minutes)	2L	The Subcommittee ***deferred*** making a recommendation pending the publication of longer follow-up including mature survival data from the AURA3 trial.
PTAC August 2020 (minutes)	1L	The Committee recommended funding ***if cost-neutral*** to current 1L pharmaceuticals in this indication, based on: • The high health need of people with lung cancer and the current availability of two effective agents in the same class funded for this indication • High quality, randomised-control trial evidence that reported benefit in PFS compared with the comparator (gefitinib or erlotinib) • Uncertain evidence regarding benefit in OS compared with the comparator
	2L	***Deferred*** pending publication and peer-review of the AURA-3 OS results
CaTSoP April 2021 (minutes)	1L	The Subcommittee recommended funding with a ***high priority***. In making this recommendation, the Subcommittee considered: • The health need of patients with EGFRm positive NSCLC and • The evidence supporting an OS benefit with osimertinib compared to first-generation TKIs with long term follow-up, in a comparable patient population
	2L	The Subcommittee recommended funding with a ***high priority***. In making this recommendation, the Subcommittee considered: • The health need of patients with EGFR T790M mutation-positive NSCLC • The evidence of a PFS benefit with osimertinib in 2L for EGFR T790M mutated NSCLC • Supporting evidence of an OS benefit from osimertinib in 2L in a comparable population • The suitability of osimertinib compared with systemic chemotherapy

3. Supplier and International Cost-Utility Analyses

3.1 Cost-Utility Analysis in Application

In the 2017 application for 2L, the supplier submitted a cost utility analysis (CUA) (A1091099) which estimates that osimertinib is cost-saving. However, in the model report (A1091100), the cost-effectiveness is claimed to be S 9(2)(b) (ii), 9(2)(ba) per QALY. This roughly translates to S 9(2)(b)(ii), 9(2)(ba)(i) & 9 per QALY or S 9(2) QALYs per $1 million invested. However, results may be misleading given:

- Use of immature overall survival data from phase II trials
- The model submitted is a global model, calibrated to the United Kingdom context, so aspects of the treatment paradigm and resource use are misleading
- The model type was partitioned survival, which is often appropriate for oncology treatments, however a Markov model was considered preferable given its greater flexibility.

No CUA was provided in the 1L application. Pharmac have therefore built two CUA models to estimate the cost-effectiveness of osimertinib for EGFRm positive NSCLC, in both the 1L and 2L settings.

3.2 International Cost-Utility Analyses

International CUAs on osimertinib for EGFRm positive NSCLC which have been identified are summarised in Table 6.

Table 6: Summary of international cost-utility analyses

International HTA Agency	Recommendation	Notes
1L		
National Institute for Health and Care Evidence (NICE – UK)	In October 2020, NICE recommended 13simertinib for the 1L treatment of locally advanced or metastatic EGFRm positive NSCLC (NICE TA654)	• Osimertinib was considered cost-effective compared with erlotinib, gefitinib and afatinib • Exact incremental cost effectiveness ratios (ICER) are confidential and not publicly available • One of the comparator treatments, afatinib, is not funded in New Zealand
Pharmaceutical benefits Advisory Committee (PBAC - Australia)	In the July 2020 PBAC meeting, osimertinib for the 1L treatment of EGFR positive NSCLC was recommended for listing (Public summary document)	• It was considered likely that osimertinib provides, for some patients, an improvement in efficacy and a reduction in toxicity compared with listed TKIs erlotinib and gefitinib • Exact ICERs are confidential and not publicly available, however the PBAC considered that the cost-effectiveness would likely be sufficient to warrant funding. • Osimertinib was already funded as a 2L treatment, so it was also one of the subsequent comparator treatments in the assessment. Some people would receive osimertinib upon disease progression while on erlotinib/gefitinib
Canadian Agency for Drugs and Technologies in Health (CADTH)	In January 2019, CADTH recommended that osimertinib for the 1L treatment of EGFR positive NSCLC be reimbursed (CADTH final recommendation) if cost-effectiveness is improved and the budget impact is addressed.	• CADTH considered that osimertinib provides a net clinical benefit compared to gefitinib and afatinib • Due to the high cost relative to the comparators, CADTH did not consider osimertinib to be cost-effective • One of the comparator treatments, afatinib, is not funded in New Zealand
2L		
NICE - UK	In October 2020, NICE recommended osimertinib for the treatment of locally advanced or metastatic EGFR T790M positive NSCLC following 1L treatment with a TKI (NICE TA653)	• The cost-effectiveness compared with platinum-based chemotherapy was considered uncertain, but likely within what NICE considers to be acceptable use of NHS resources • Exact ICER results are confidential and not publicly available, however NICE considered that the cost-effectiveness would likely be acceptable
PBAC - Australia	In the November 2018 PBAC meeting, osimertinib for EGFR T790M positive NSCLC following 1L treatment with	• It was considered likely that osmiertinib provides, for some patients, an improvement in efficacy and a reduction in toxicity compared with platinum-based chemotherapy

	a TKI was recommended for listing (Public Summary document)	• Exact ICERs are confidential and not publicly available
CADTH	In May 2017, CADTH recommended that osimertinib for EGFR T790M positive NSCLC following 1L treatment with a TKI be reimbursed (CADTH Reimbursement Recommendation) if cost-effectiveness can be improved to an acceptable level	• CADTH considered that osimertinib provides a net clinical benefit compared to platinum-based chemotherapy • Due to the high cost of relative to the comparators, CADTH did not consider osimertinib to be cost-effective

Pharmac staff consider that these results are generally not applicable to the New Zealand clinical and pharmaceutical funding environment due to the difference in the comparator treatments used in most of the analyses, and differences in the health sectors between countries.

4. Pharmac Cost-Utility Analysis

A CUA was undertaken to estimate the cost-effectiveness of osimertinib for EGFRm positive NSCLC in the 1L setting and in the 2L setting for those who have developed the T790 mutation on 1L treatment.

4.1 Scope of Analysis

The analysis was undertaken from the health system perspective.

4.1.1 Target Population

The target populations for this analysis for 1L and 2L are as follows:

- **1L**: People with Stage lllb or Stage lV, non-squamous NSCLC, who have the EGFR tyrosine kinase mutation, and who are either treatment naïve or have discontinued treatment on a first generation (1st gen.) TKI - either gefitinib or erlotinib - due to intolerance and do not have progressed disease
- **2L**: People with locally advanced or metastatic NSCLC, who have the EGFR tyrosine kinase mutation with T790M mutation and have progressed during 1L treatment with a TKI.

4.1.2 Comparator

The comparators in the analysis are detailed below - see Figure 1 for a summary:

- **1L**: For treatment naïve patients: erlotinib, one 150 mg tablet daily or gefitinib, one 250 mg tablet daily, until disease progression or unacceptable toxicity. Pharmac dispensing data (Pharmac Qlik: Patients -> Erlotinib or gefitinib 2018/19 to 2020/21) indicates approximately 63% of people with EGFRm positive NSCLC receive erlotinib as 1L treatment, with the remaining ~37% receive gefitinib.
    - Upon disease progression, 60% of patients receive platinum-based chemotherapy as 2L treatment and 30% of those people proceed to docetaxel (75mg/m^2 3 weekly, 90 min infusion) as 3L treatment. Those who do not receive either of these treatments instead receive best supportive care (BSC).
- **2L**: Platinum-based chemotherapy as 2L treatment followed by 3L docetaxel following disease progression. 60% of people are assumed to receive chemotherapy, with the remaining 40% starting on best supportive care. As in the 1L model, 30% of people who receive 2L chemotherapy proceed to docetaxel (75mg/m^2 3 weekly, 90 min infusion) as 3L treatment.

The proportion of people receiving chemotherapy and docetaxel was informed by advice from CTAC (2022-10-14 CTAC record, para 4.47) that approximately 30% of people with NSCLC (with no confirmed EGFR mutation) would receive docetaxel after progression on chemotherapy, with the remainder receiving no active treatment due to treatment fatigue and the high toxicity of docetaxel. It was considered appropriate to use this estimate for those with EGFR mutations as well, since docetaxel and chemotherapy are indicated as subsequent treatments for both types of NSCLC.

The proportion of people who received 2L chemotherapy was assumed to be 60% - higher than docetaxel but not 100% of the group who progressed on osimertinib or a first generation TKI. Given the considerable uncertainty around this proportion, it was tested in sensitivity analysis. Those who do not receive these subsequent treatments move to BSC.

Advice indicates that platinum-based chemotherapy is an appropriate 2L comparator in the New Zealand context (CaTSoP Record April 2021). The dosing regimen for platinum-based chemotherapy is assumed to be the same as the regimen used to treat other types of NSCLC. It consists of three-weekly carboplatin or cisplatin with pemetrexed. More detail on the dosing regimen can be found in the pharmaceutical costs subsection (section 4.5.1).

4.2 Model Structure

Two Markov models were constructed to model each 1L and 2L use of osimertinib.

4.2.1 Time Horizon

The CUA used a lifetime time-horizon to fully capture costs and health outcomes over a representative patient's lifetime. Each Markov cycle was one week to account for the duration of the various chemotherapy regimens. A half-cycle correction was applied.

All costs and benefits were discounted at 3.5%.

4.2.2 Model Structure

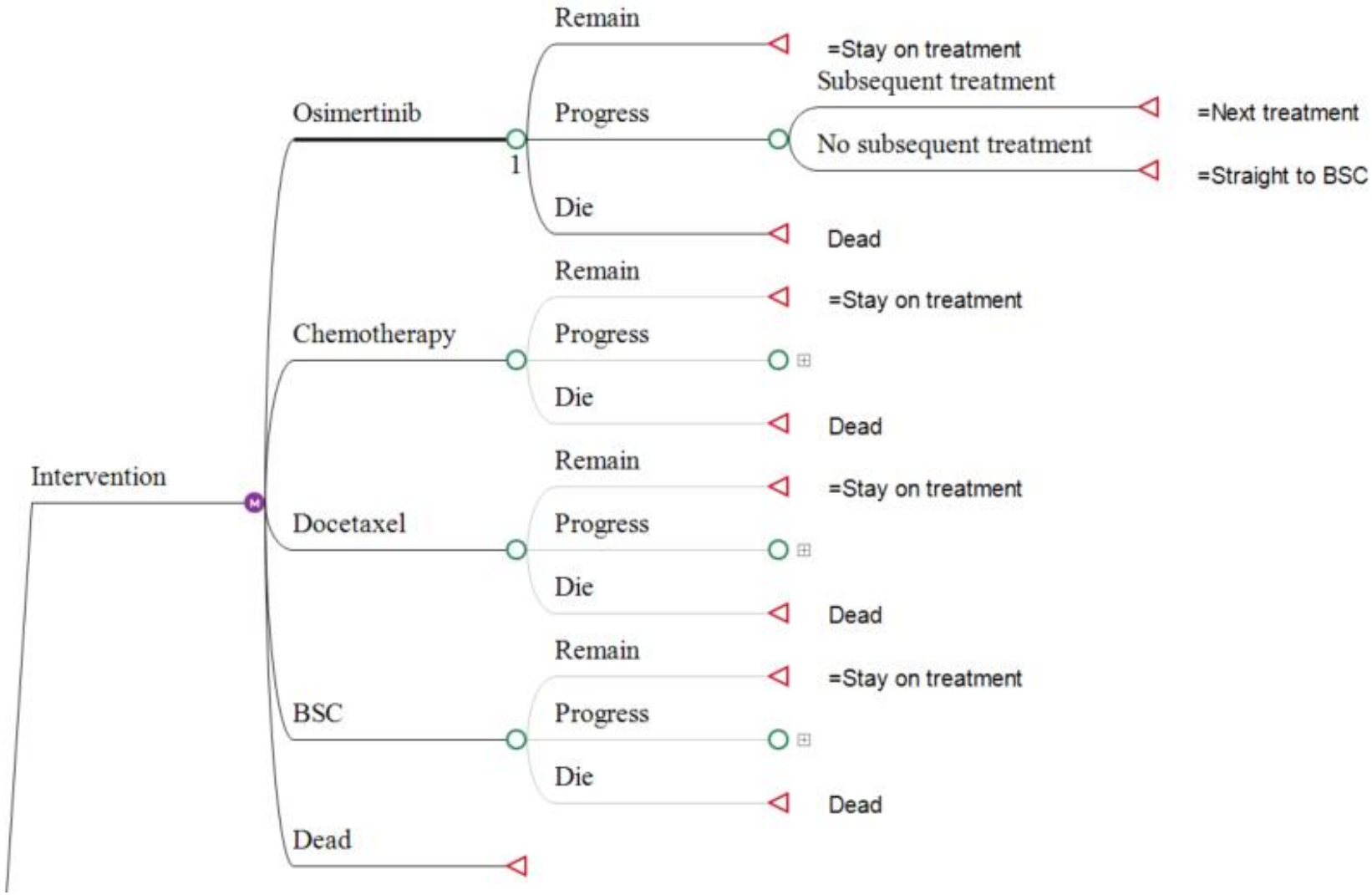
The Markov models include the following health states:

- Progression-free survival: The individual's disease has not progressed while on treatment. This is not included in the 2L model since people only start osimertinib treatment once the disease has already progressed.
- Progressed disease 1: The individual's disease has progressed once
- Progressed disease 2: The individual's disease has progressed two or more times.
- Dead: The individual has died.

People move to each of these health states based on transition probabilities which depend on the treatment they receive (osimertinib, erlotinib/gefitinib, chemotherapy, docetaxel and best supportive care). These probabilities are detailed in the following section. Those whose disease does not progress remain on osimertinib treatment, while people who experience disease progression discontinue and move to the next-line of treatment, as outlined in the PICO tables. People can move to the dead state from any other health state.

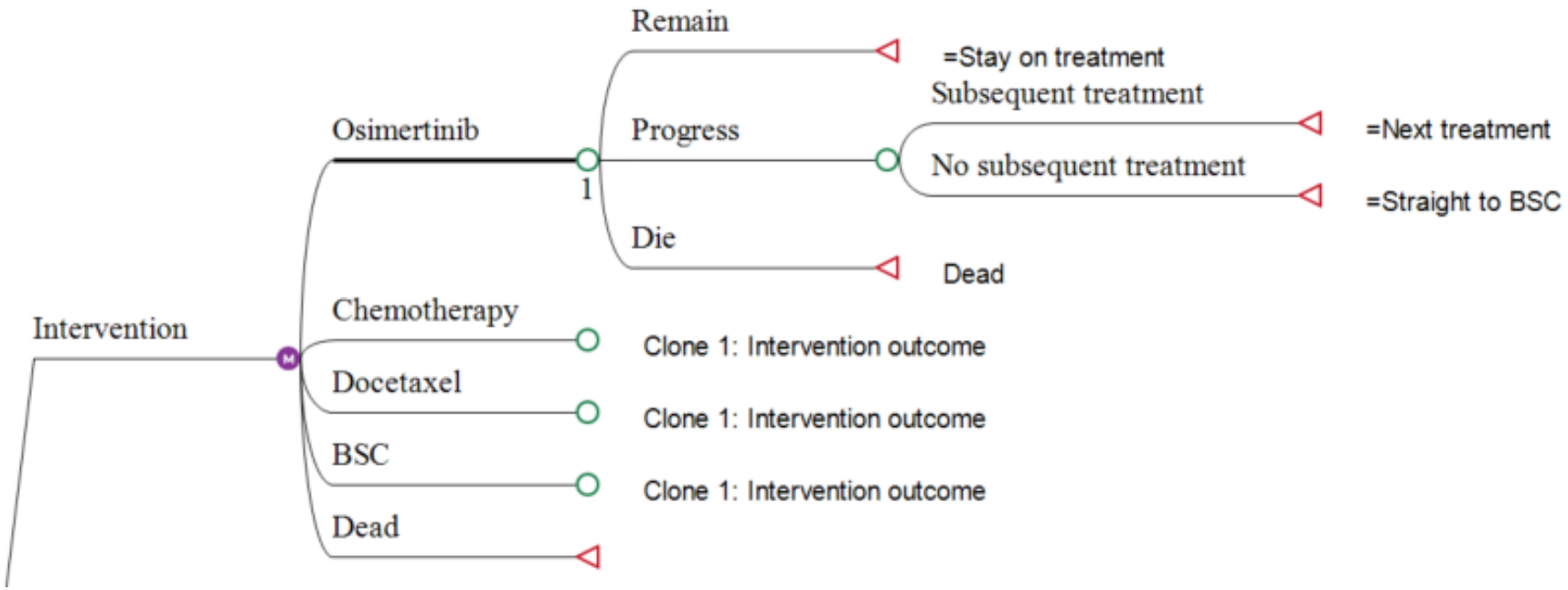
Figure 2 shows a branch of the 1L model, while Figure 3 shows a branch of the 2L model.

Figure 2: 1L model structure



Note that the comparator strategy of the 1L model is the same except for the first branch, which is first generation TKI treatment. Note that there is a zero probability of progression on BSC, the 'Progress' node is an artefact of the clone branch only.

Figure 3: 2L model structure



Note that the comparator strategy of the 2L model is the same other than the osimertinib branch, which it does not include since people start on chemotherapy.

4.3 Transformation and Extrapolation of Clinical Evidence

This economic model primarily uses evidence derived from the FLAURA and AURA3 trials, as detailed in Table 3 (1L) and Table 4 (2L). Some parameters were estimated using other evidence, since the key trials were not considered appropriate for some elements of the model. The sources for the clinical parameters are summarised in Table 7 and Table 8 below.

Table 7: Clinical parameters – 1L model

Input	Source(s)
OS	
Probability of death in intervention arm	FLAURA OS update, figure 2 (Ramalingam et al. 2020)
Probability of death in comparator arm	Lux-Lung 7 trial, figure 1 (Paz-Ares et al., Annals of Oncology, 2017: 28:270-277.). Compares afatinib (another TKI) to gefitinib in people with EGFRm positive NSCLC
Background mortality	NZ period life tables, 2017-2019. Objective ID A1497544
PFS	
Probability of progression on osimertinib treatment	FLAURA trial, figure 1A (Soria et al. 2018)
Probability of progression on 1st gen. TKI treatment	
Probability of progression on chemotherapy	AURA3 trial, figure 1A (Mok et al. N Engl J Med. 2017;376:629-40)
Probability of progression on docetaxel treatment	Assumed to be the same as chemotherapy in the base case

Table 8: Clinical parameters – 2L model

Input	Source(s)
OS	
Probability of death in intervention arm	AURA3 OS update, figure 2A (Papadimitrakopoulou et al. Ann Oncol. 2020;31:1536-44)
Probability of death in comparator arm	IMPRESS trial, figure 3 (Mok et al., J Clin Onc, 2017: 35(36)). Compares gefitinib plus chemotherapy to placebo plus chemotherapy in people with EGFRm positive NSCLC
Background mortality	NZ period life tables, 2017-2019
PFS	
Probability of progression on osimertinib treatment	AURA 3 trial, figure 1A (Mok et al. N Engl J Med. 2017;376:629-40)
Probability of progression on chemotherapy	AURA 3 trial, figure 1A
Probability of progression on docetaxel treatment	Assumed to be the same as chemotherapy in the base case

The probability of death and progression was estimated by fitting exponential functions to the Kaplan-Meier evidence provided in the trials. A single exponential function for each survival curve did not prove to be a good fit, although the R-squared (a crude measure of goodness-of-fit, where 1 indicates a perfect fit and 0 indicates no correlation at all) values were mostly above 0.95, visual inspection indicated that there was often a systematic underestimate of death/progression in the early months, and an overestimate in the later months. To mitigate this systematic difference, piecewise exponential functions were fitted to the Kaplan-Meier curves based on visual inspection and were adjusted to maximise the R-squared value. The

timepoint at which a different curve was fitted was varied during curve fitting, and the time point was selected based on visual inspection and the R-squared value of the resulting piece-wise curves.

This approach broadly captures the likelihood of death and progression from the available evidence, and is considered reasonable given the insensitivity of model results to changes in these probabilities (see section 4.7 on sensitivity analysis). If commercial considerations change and results become more sensitive to changes in these probabilities, then it may be necessary to revisit the approach, for instance through the use of hazard functions or other parametric distributions.

Background mortality estimates were used to ensure that mortality estimates for people with EGFRm positive NSCLC were realistic given their age.

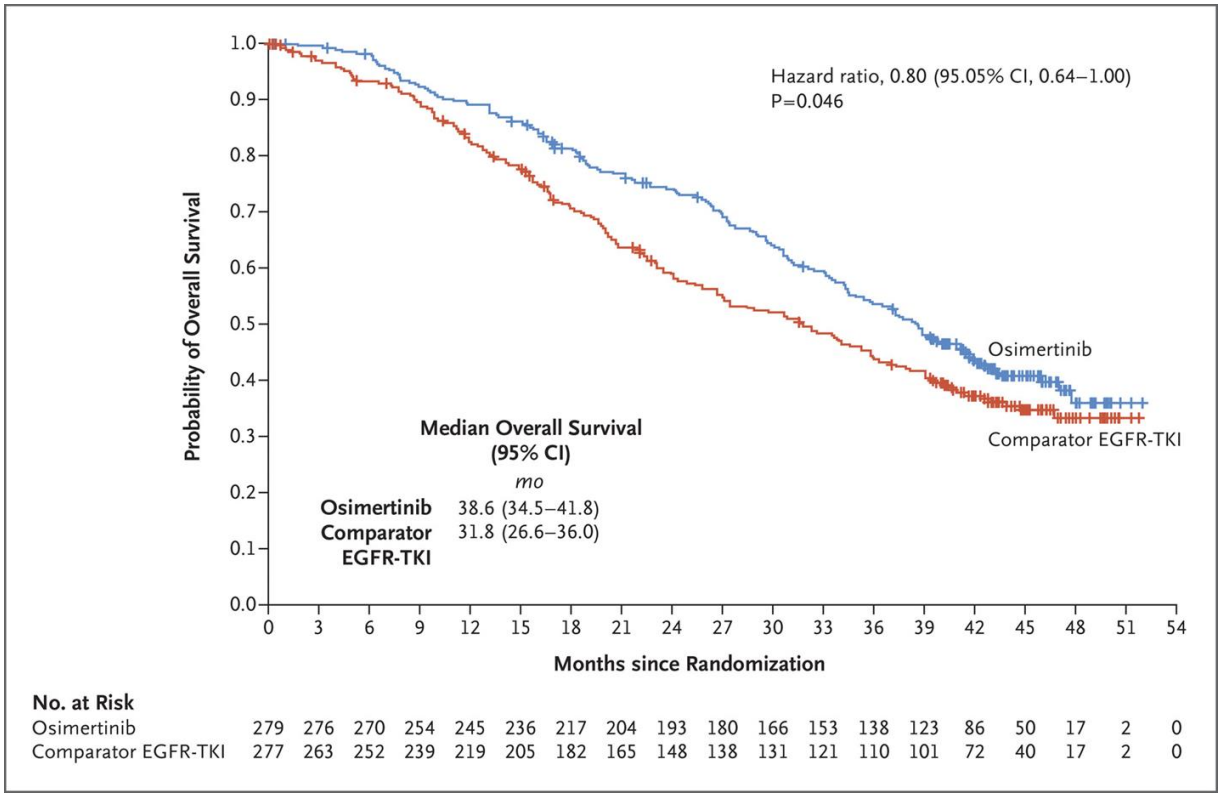
Adverse events, particularly those of grade 3+ severity, tended to be higher in the comparator arms of the trials than in the osimertinib arms, although these differences were not always statistically significant. In the base case for each model, no difference in adverse events was included. Higher rates of adverse events in the comparator arm were tested in sensitivity analysis.

4.3.1 1L Overall Survival

Intervention

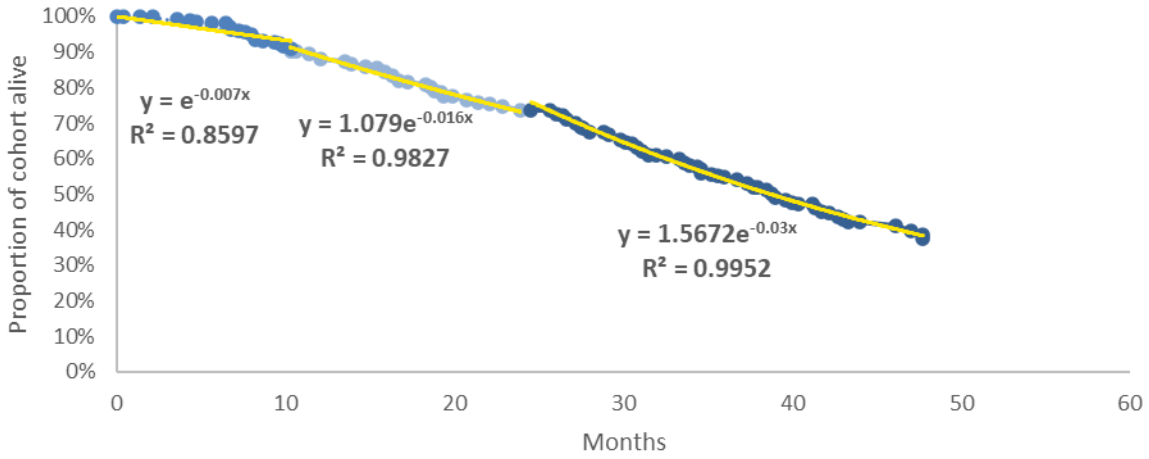
The probability of death for people in the intervention arm of the 1L model was estimated using the Kaplan-Meier OS curve for osimertinib from figure 2 the FLAURA OS update. This curve is shown in Figure 4 below.

Figure 4: Kaplan-Meier OS curve (proportion alive by month) from FLAURA trial



This curve was then plot-digitised and fitted with three piecewise exponential curves. Three curves were used since splitting the exponential into three fit the data better than a single curve or splitting the exponential in two. The digitised data points and fitted exponential curve are depicted in Figure 5 below. The figure also shows the R-squared value for each curve, which is a crude measure of goodness of fit, as well as the equation for each exponential.

Figure 5: Exponential approximation of Osimertinib OS curve from FLAURA trial



The exponential equations were then used to estimate the monthly probability of death using the following equation based on page 36 of the Prescription for Pharmacoeconomic Analysis (PFPA), where r is the exponential rate and t is the cycle length (1):

$$Probability\ of\ death\ on\ Osimertinib\ 1L = 1 - e^{-rt}$$

For example, the probability of death over the first 10 months was estimated via the equation below.

$$Probability\ of\ death\ on\ Osimertinib\ 1L = 1 - e^{-0.007} = 0.70\%$$

This calculation was repeated for the other two curves, resulting in a monthly probability of death from 10 months to 24 months of 1.59%, and a probability of death of 2.96% thereafter. These probabilities were converted into weekly probabilities using the 'probtoprob' function in TreeAge to align with the weekly cycle length.

A sensitivity analysis was undertaken, given the significant uncertainty associated with the OS, in the absence of a direct treatment comparison in a relevant population. A scenario analysis was run based on the HR from the FLAURA trial. This was considered a conservative estimate of treatment effect on which to base a scenario analysis, given the crossover in the comparator arm.

Hence, to approximate the likely range of the mortality rates associated with osimertinib, the percentage change in the HR resulting from adding or subtracting one standard error (calculated – see Objective ID A1635336) was calculated, and applied to the mortality rates above. As a result, the rate was increased by 12.5% to define a higher estimate and decreased by 11.3% to define a lower estimate. Further details can be found in the analysis workbook. It is acknowledged that this approach is limited by the fact that it is unclear if the proportional hazards assumption held in the FLAURA trial. It is also unclear the extent to which the HR is an underestimate of the treatment effect, so the scenario may be highly conservative if the crossover significantly impacted the result.

Comparator

The probability of death for people in the comparator (1st gen. TKI) arm of the 1L model was estimated using the Kaplan-Meier OS curve for gefitinib from figure 1 of the Lux-Lung 7 trial. This curve was deemed more appropriate to use than that of the comparator arm from the FLAURA OS update for a number of reasons:

- In the FLAURA trial, 47% of people in the comparator arm received osimertinib upon disease progression, which in NZ was not funded as a 2L treatment at the time of writing. Therefore, the comparator arm of FLAURA likely overestimates OS compared to what would be expected in NZ.
- In the Lux-Lung 7 trial, some people received osimertinib after discontinuing treatment, but this was a small proportion (11.3%, see table 1 in Lux-Lung 7 publication) and the impact of this subsequent treatment is tested in the sensitivity analysis as part of a two-way sensitivity analysis in which an estimate of probability of progression without osimertinib crossover was tested alongside other key parameters.
- Based on Pharmac dispensing data (Pharmac Qlik: Patients -> Erlotinib or gefitinib 2018/19 to 2020/21), approximately 63% of people with EGFRm positive NSCLC receive erlotinib as 1L treatment, with the remaining ~37% receiving gefitinib.
- Evidence (Burotto et al., The Oncologist, 2015: 20 (4): 400-410.) and clinical advice (CaTSoP meeting record April 2021. Para 7.18.2) suggest that both TKIs are equivalent in terms of efficacy, so the gefitinib curve was considered appropriate to use to represent the mixed current comparator in the NZ setting.

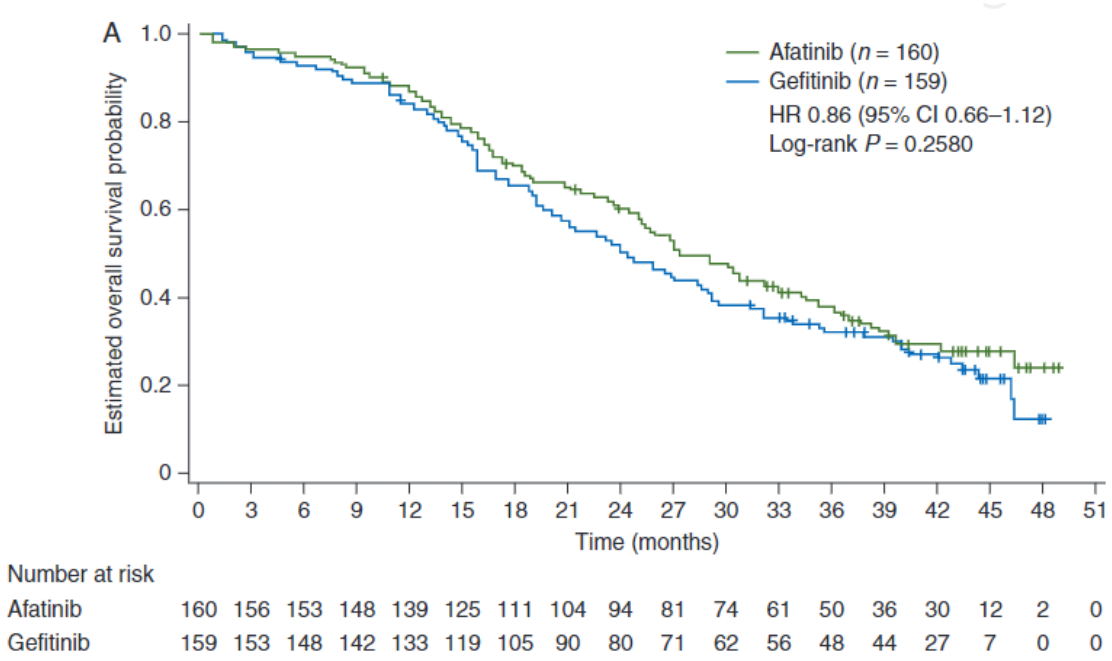
It is acknowledged that a naïve rather than a head-to-head comparison may introduce bias due to differences in the trial populations. In this case, the key trials were fairly similar in terms of patient characteristics:

- Both trials were in people with previously untreated, metastatic EGFRm positive NSCLC
- The mean age in the Lux-Lung 7 gefitinib arm was 63 (Clinical trial NCT01466660), compared to a median (mean not reported in publication) was 64 in FLAURA
- In addition, median PFS in the gefitinib arm was 10.9 months, which is comparable to the median PFS of the comparator arm (erlotinib/gefitinib) in FLAURA, which was 10.2 months

Noting the similar populations and median PFS compared to the AURA3 trial, internal advice (A1633004) was that it was reasonable to use the Kaplan-Meier OS curve from the gefitinib arm to inform OS in the comparator arm of the model, since the significant crossover undermined the applicability of OS evidence from the FLAURA trial.

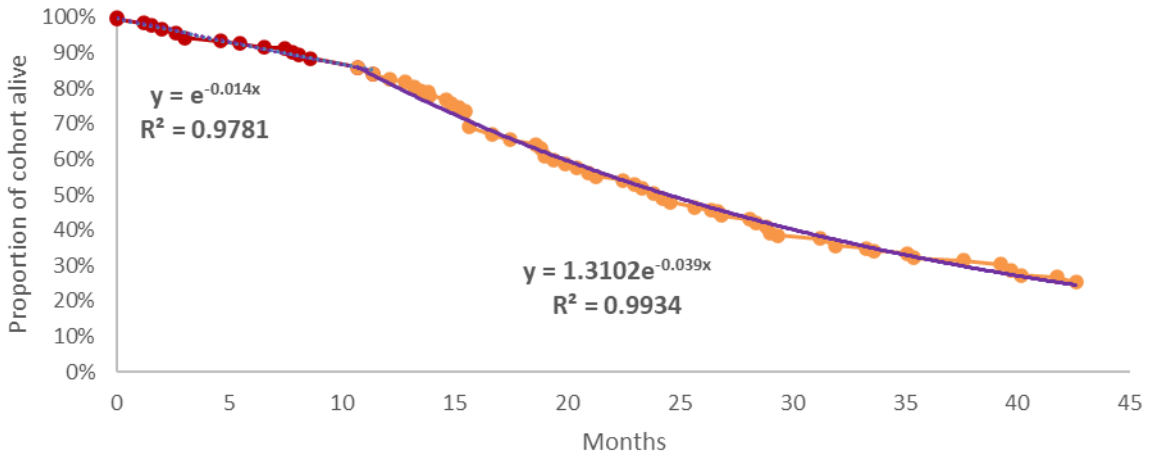
This curve is shown in Figure 6 below.

Figure 6: Kaplan-Meier OS curve (proportion alive by month) from Lux-Lung 7 trial



This curve was then plot-digitised and fitted with two exponential curves. Two curves were used since splitting the exponential fit the data better than a single curve. The digitised data points and fitted exponential curve are depicted in Figure 7 below.

Figure 7: Exponential approximation of gefitinib OS curve from Lux-Lung 7



The monthly probability of death was then estimated, using rates derived from the exponential functions, to be 1.39% in the first 10 months and 3.82% thereafter. These probabilities were converted into weekly probabilities using the 'probtoprob' function in TreeAge.

Summary

The overall survival probabilities used in the 1L model are summarised in Table 9.

Table 9: Overall survival probabilities in 1L model

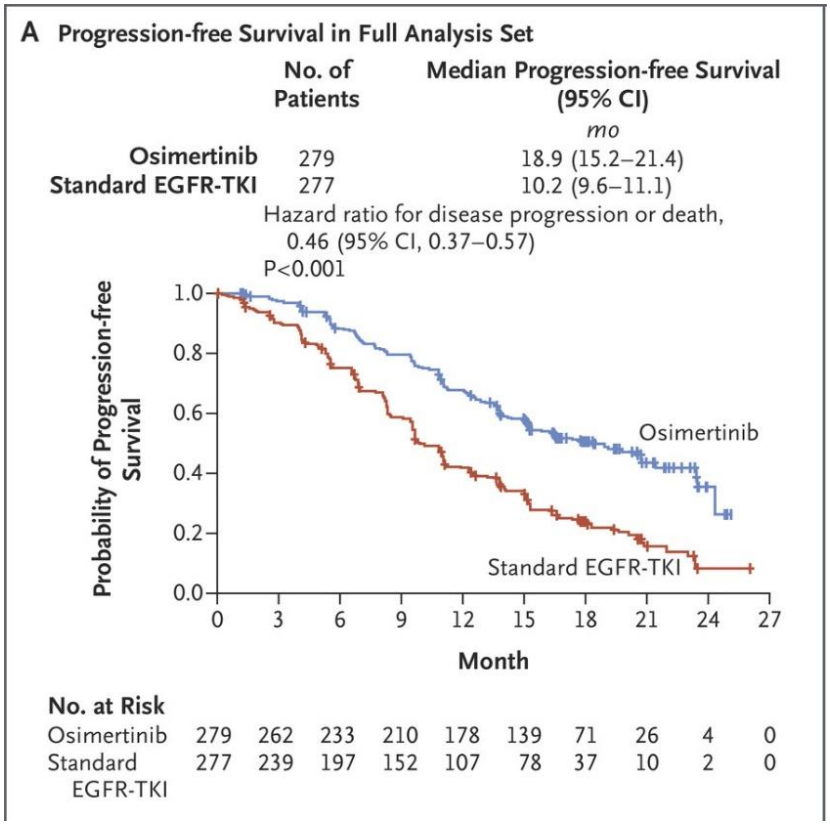
Time period	Monthly probability of death	
	Intervention	Comparator
First 10 months	0.70%	1.39%
Months 10-24	1.59%	3.82%
Months 24+	2.96%	3.82%

4.3.2 1L Progression free Survival

Osimertinib

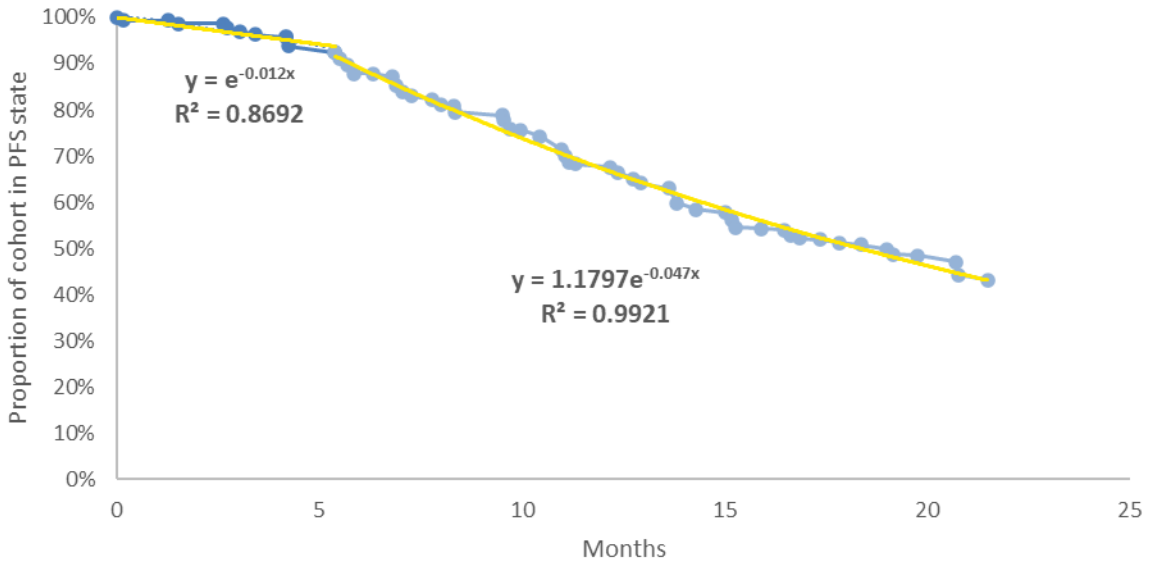
The probability of progression for people on osimertinib treatment in the 1L model was estimated using the Kaplan-Meier PFS curve for osimertinib in the full analysis population, from figure 1A in the FLAURA trial. This curve is shown in Figure 8 below.

Figure 8: Kaplan-Meier PFS curve from FLAURA trial



This curve was then plot-digitised and fitted with two exponential curves. Two curves were used since splitting the exponential fit the data better than a single curve. The digitised data points and fitted exponential curve are depicted in Figure 9 below.

Figure 9: Exponential approximation of osimertinib PFS curve from FLAURA trial



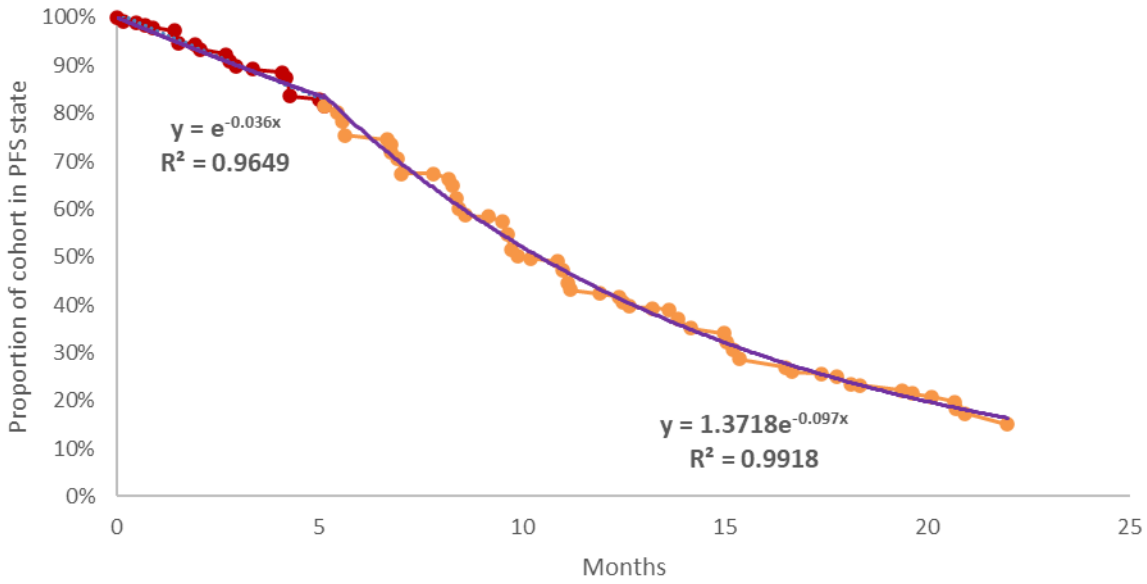
The monthly probability of progression was then estimated, using rates derived from the exponential functions, to be 1.19% in the first 5 months and 4.59% thereafter. These probabilities were converted into weekly probabilities using the 'probtoprob' function in TreeAge.

First generation TKIs

The probability of progression for people on 1st gen. TKI treatment in the 1L model was estimated using the Kaplan-Meier PFS curve for 'standard EGFR TKI' (erlotinib or gefitinib) from figure 1A in the FLAURA trial, as depicted in Figure 8 on the previous page.

This curve was then plot-digitised and fitted with two exponential curves. The digitised data points and fitted exponential curves are depicted in Figure 10 below.

Figure 10: Exponential approximation of 1st gen. PFS curve from FLAURA trial

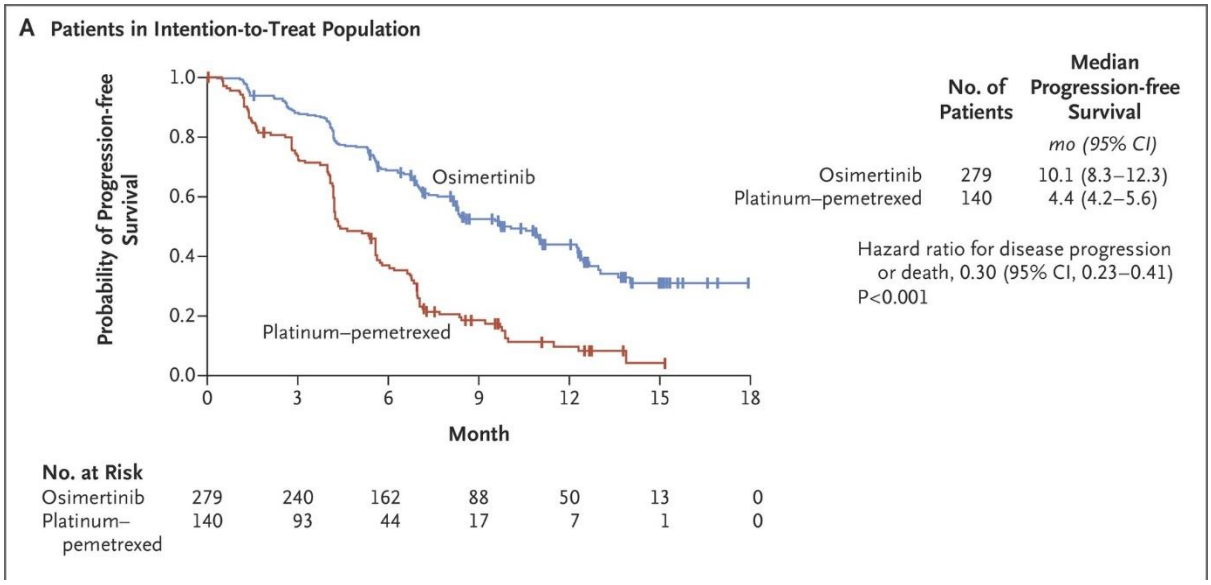


The monthly probability of progression was then estimated using the rates derived from the exponential function to be 3.54% in the first 5 months and 9.24% thereafter. These probabilities were converted into weekly probabilities using the 'probtoprob' function in TreeAge.

Chemotherapy

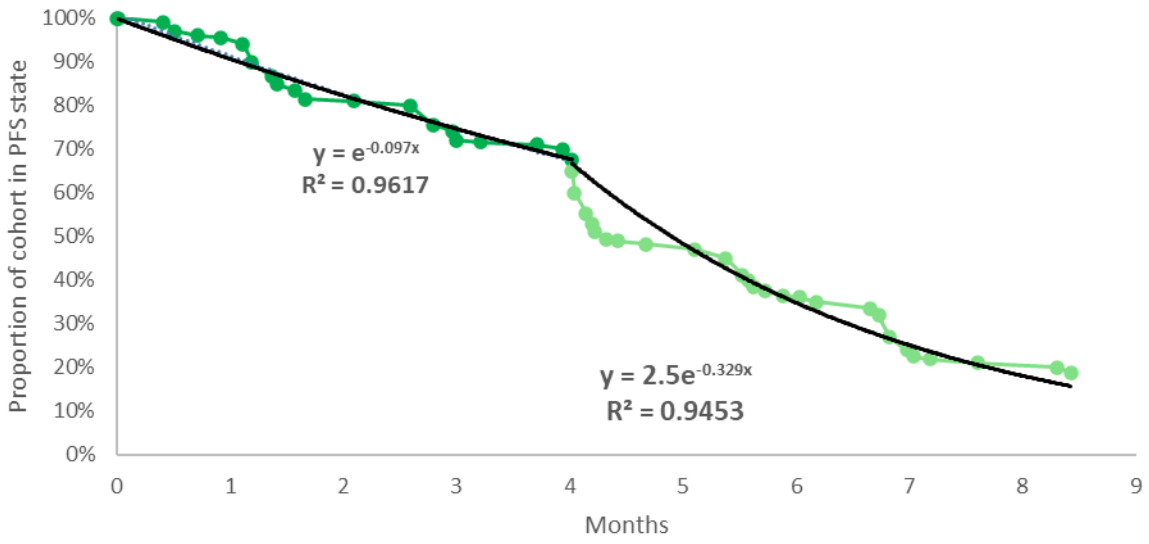
The probability of progression for people on 2L chemotherapy in the 1L model was estimated using the Kaplan-Meier PFS curve for chemotherapy (platinum-pemetrexed, a type of platinum-based chemotherapy) from figure 1A in the AURA3 trial (osimertinib relative to chemotherapy in 2L setting). This curve is shown in Figure 11 below.

Figure 11: Kaplan-Meier PFS curves from AURA3 trial



This curve was then plot-digitised and fitted with two exponential curves. The proportion of the curve beyond 9 months was not digitised due to the low numbers at risk in the platinum-pemetrexed arm after this period. The digitised data points and fitted exponential curve are depicted in Figure 12 below.

Figure 12: Exponential approximation of chemotherapy PFS curve from AURA3 trial



A limitation of this approach is the visually poor fit of the exponential curve to the events taking place between the fourth and fifth months of follow up. Alternative fitted curves were tested, since a moderate number of patients were still at risk at this time point, so the sudden decline was considered plausible. It was speculated that this may have been because of the follow up milestones, which may have related to the duration of chemotherapy or other treatment monitoring or cessation. However, ultimately the fitted curve was considered an acceptable approximation and the impact on model results was considered if anything conservative, as it would favour the comparator arm.

The monthly probability of progression was then estimated using the rates derived from the exponential function, to be 9.24% in the first 5 months and 28.04% thereafter. These probabilities were converted into weekly probabilities using the 'probtoprob' function in TreeAge.

Docetaxel

There is limited evidence for the efficacy of docetaxel in treating those with EGFRm positive NSCLC. One trial (Hanna et al., J Clin Onc 2004; 22:1589-1597) indicates similar efficacy (but worse safety) compared to pemetrexed alone in patients with previously treated advanced NSCLC (not specific to the EGFRm positive population). There was no statistically significant difference in OS or PFS - Median OS was 8.3 months in the pemetrexed arm and 7.9 months in the docetaxel arm, while median PFS was 2.9 months in both arms. Based on this, the model assumes the same PFS probabilities as chemotherapy in the model base case. This is a limitation in the analysis, however, it is not impactful given that only a small proportion of people in the model receive docetaxel. In sensitivity analysis, the impact of this assumption is varied.

Summary

The PFS probabilities used in the 1L model are summarised in Table 10.

Table 10: Probability of progression in 1L model

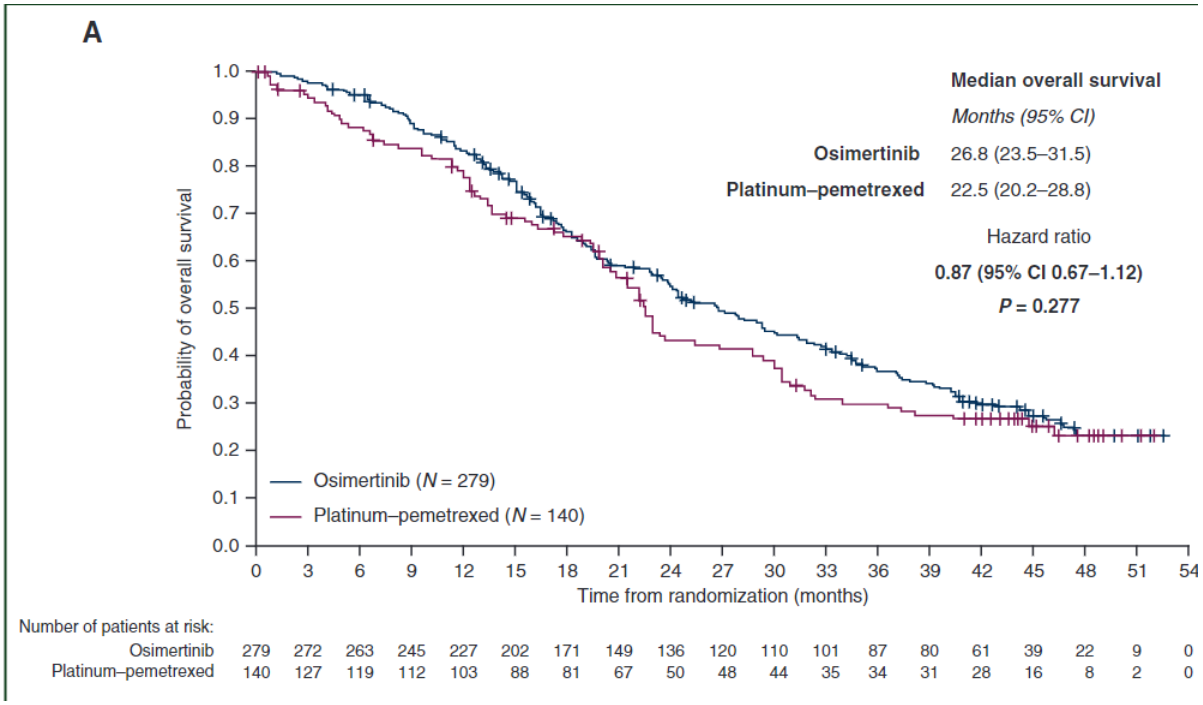
Time period	Monthly probability of progression			
	Osimertinib	**1st gen. TKI**	**Chemotherapy**	**Docetaxel**
First 4 months	1.19%	3.54%	9.24%	9.24%
Months 4-5	1.19%	3.54%	28.04%	28.04%
Months 5+	4.59%	9.24%	28.04%	28.04%

4.3.3 2L Overall survival

Intervention

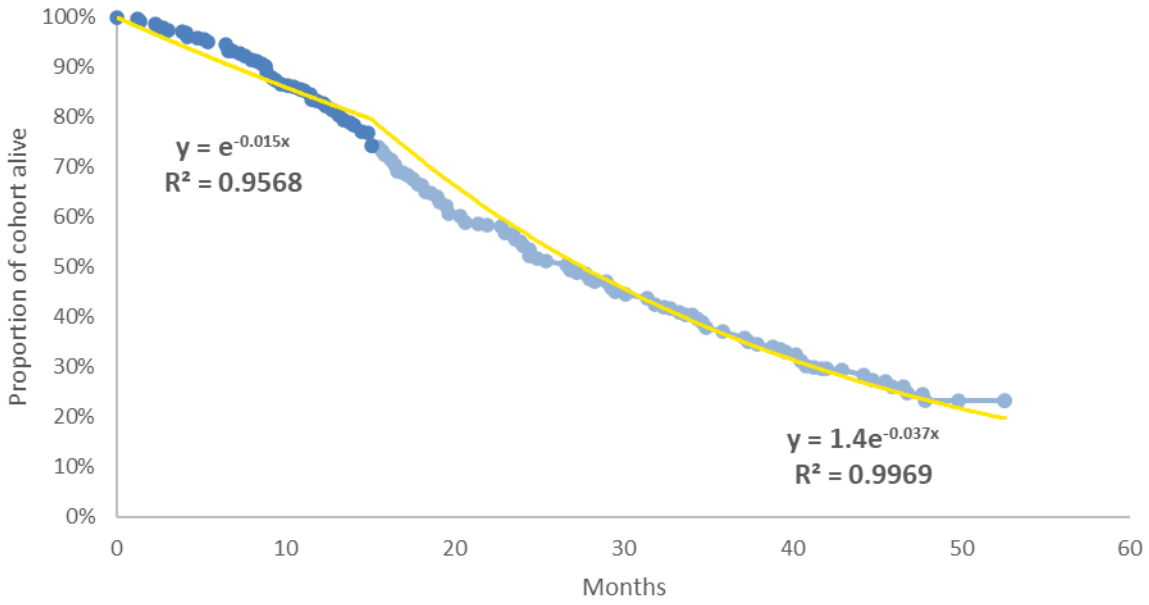
The probability of death for people in the intervention arm of the 2L model was estimated using the Kaplan-Meier OS curve for osimertinib from figure 2A in the AURA3 OS update. This curve is shown in Figure 13 below.

Figure 13: Kaplan-Meier OS curve (proportion alive by month) from AURA3 OS update



This curve was then plot-digitised and fitted with two exponential curves. Two curves were used since splitting the exponential fit the data better than a single curve. The digitised data points and fitted exponential curve are depicted in Figure 14 below.

Figure 14: Exponential approximation of osimertinib OS curve from AURA3 OS update



The monthly probability of death was then estimated, using the rates derived from the exponential function, to be 1.49% in the first 15 months and 3.63% thereafter. These probabilities were converted into weekly probabilities using the 'probtoprob' function in TreeAge.

A sensitivity analysis was undertaken, given the significant uncertainty associated with the OS, in the absence of a direct treatment comparison in a relevant population. A scenario analysis was run based on the HR from the AURA3 trial, using the same approach as described in *Section 4.3.1 – Intervention for 1L OS*. This was considered a conservative estimate of treatment effect on which to base a scenario analysis, given the crossover in the comparator arm.

As a result, the 2L OS mortality rate associated with osimertinib was increased by 13.8% to define a higher estimate and decreased by 12.6% to define a lower estimate. Further details can be found in the analysis workbook (see Objective ID A1635336). It is acknowledged that this approach is limited by the fact that it is unclear if the proportional hazards assumption held in the AURA3 trial. It is also unclear the extent to which the HR is an underestimate of the treatment effect, so the scenario may be highly conservative if the crossover significantly impacted the result.

Comparator

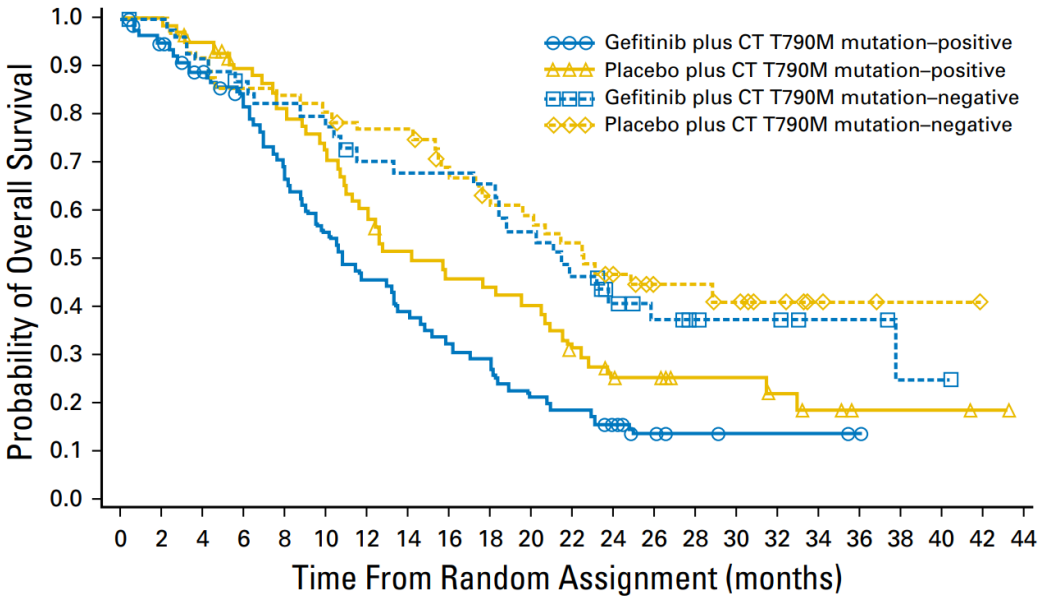
The probability of death for people in the comparator (chemotherapy) arm of the 2L model was estimated using the Kaplan-Meier OS curve for the placebo plus chemotherapy, T790M positive group from figure 3 of the IMPRESS trial. This curve was deemed more appropriate to use than that of the comparator arm from the AURA3 OS update, since in the AURA3 trial, 73% of people in the platinum-pemetrexed arm crossed-over to receive osimertinib, which does not represent the comparator treatment paradigm in NZ. The crossover likely means that OS would be overestimated in the chemotherapy arm, and the treatment benefit from osimertinib would be underestimated.

As noted in the discussion of the 1L evidence, indirect naïve comparisons can cause bias, however, as with 1L, patient populations were comparable between these two trials. It is noted that the population in the IMPRESS trial is slightly younger (mean age 56 compared to a median age 62 in AURA3), which may mean the OS in the chemotherapy arm is slightly overestimated, but by a likely smaller magnitude than the overestimate resulting from crossover to osimertinib. In both trials, people were EGFRm positive and reported OS for people with T790M mutations following 1L gefitinib.

The AURA3 OS update did provide a crossover-adjusted hazard ratio of death of 0.54, but the 95% confidence interval easily crossed 1 (95% CI 0.18-1.60), reflecting the large amount of uncertainty associated with this estimate. This was considered likely due to the level of adjustment required since such a large proportion of the population crossed over, or possibly due to the small sample size. Despite the uncertainty, internal advice was that the HR should still be tested in sensitivity analysis given that it was available and otherwise the PICO of the trial was appropriate for analysis (A1633004).

The OS curves from the IMPRESS trial are displayed in Figure 15.

Figure 15: Kaplan-Meier OS curves (proportion alive by month) from IMPRESS trial

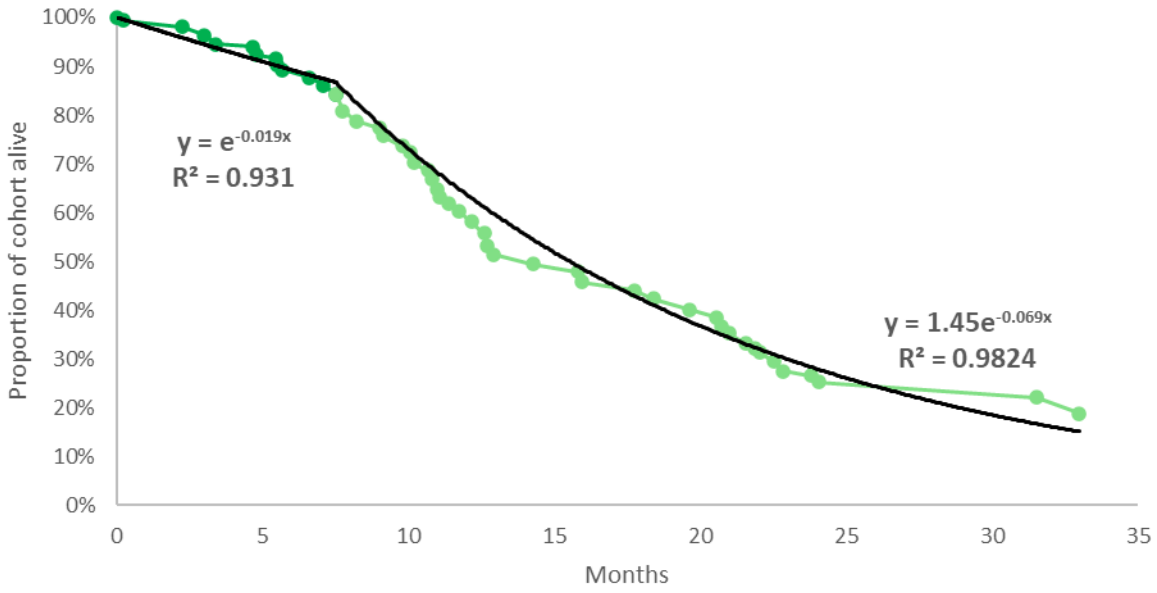


No. at risk:

Gefitinib plus CT T790M mutation–positive	81	74	66	61	49	40	33	28	23	21	15	13	9	5	3	2	2	2	1	0	0	0	0
Placebo plus CT T790M mutation–positive	61	61	57	51	46	40	34	28	25	24	22	16	12	11	8	8	6	4	2	2	2	1	0

This curve was then plot-digitised and fitted with two exponential curves. Two curves were used since splitting the exponential fit the data better than a single curve, noting that the exponential may overestimate the proportion alive slightly between months 10 and 15. The digitised data points and fitted exponential curve are depicted in Figure 16 below.

Figure 16: Exponential approximation of chemotherapy T790M + OS curve from IMPRESS trial



The monthly probability of death was then estimated, using the rates derived from the exponential function, to be 1.88% in the first 7.5 months and 6.67% thereafter. These

probabilities were converted into weekly probabilities using the 'probtoprob' function in TreeAge.

Summary

The overall survival probabilities used in the 2L model are summarised in Table 11

Table 11: Overall Survival Probabilities in 2L model

Time period	Monthly probability of death	
	Intervention	Comparator
First 7.5 months	1.49%	1.88%
Months 7.5-15	1.49%	6.67%
Months 15+	3.63%	6.67%

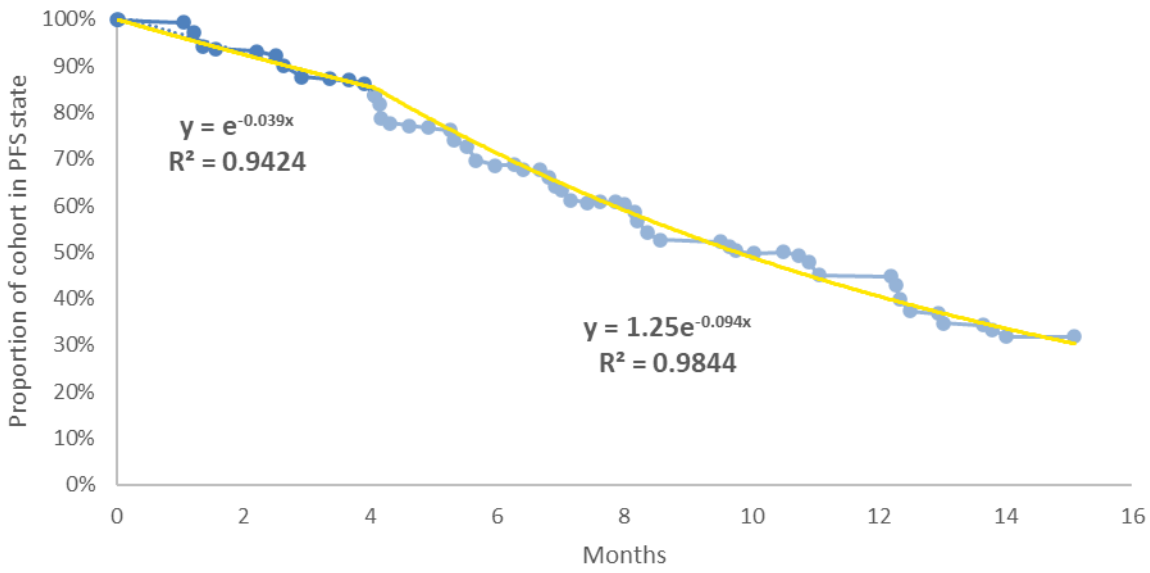
4.3.3 2L Progression free survival

Osimertinib

The probability of progression for people on osimertinib treatment in the 2L model was estimated using the Kaplan-Meier PFS curve for platinum pemetrexed from figure 1A in the AURA3 trial. This curve is shown in Figure 11 earlier in this section.

This curve was then plot-digitised and fitted with two exponential curves. The digitised data points and fitted exponential curve are depicted in Figure 17 below.

Figure 17: Exponential approximation of osimertinib PFS curve from AURA3 trial



The monthly probability of progression was then estimated using the exponential rates to be 3.82% in the first 4 months and 8.97% thereafter. These probabilities were converted into weekly probabilities using the 'probtoprob' function in TreeAge.

Chemotherapy

The probability of disease progression while on chemotherapy is the same as in the 1L model, since in both cases people are receiving chemotherapy as a 2L treatment.

Docetaxel

The probability of disease progression while on docetaxel is the same as in the 1L model, since in both cases people are receiving docetaxel as a 2L treatment.

Summary

The PFS probabilities used in the 2L model are summarised in Table 12.

Table 12: Probability of progression in 2L model

Time period	Monthly probability of progression		
	Osimertinib	Chemotherapy	Docetaxel
First 4 months	3.82%	9.24%	9.24%
Months 4+	8.97%	28.04%	28.04%

4.4 Health-Related Quality of Life

The model applies HRQOL utility weights to time spent in each health state. The utility values used in the base case are sourced from a systematic literature review (Shor et al., Value in Health 2018; 21(S1): S35-36) that examined patient-reported HRQOL among people with EGFRm positive NSCLC. The utility values used in the base case are shown in Table 13.

Table 13. Utility values

Health State	Utility weight	Notes
Progression-free disease (1L)	0.815	Mid-point of reported pre-progression utility values Applied only in 1L, since people in the 2L model have already progressed
Progressed disease 1 (2L)	0.750	Upper bound of progressed disease utility values
Progressed disease 2 (3L)	0.680	Lower bound of progressed disease utility values to capture falling HRQoL due to second progression
Dead	0	-

Internal advice (A1633004) recommended that multiple health states and associated utility values for progressed disease should be included in modelling, which Shor et al. reported. Though a range of utility values for progressed disease was reported, rather than specific utilities associated with successive progressed disease states, the range provided by Shor et al. was used to define the values in the first and second progressed disease states.

These values were used in the base case because:

- They were based on a systematic literature review
- They were relatively conservative among the other estimates (see Sensitivity analysis)
- The lower utility weights assigned to subsequent progressions (the lower bound of the range reported) appeared consistent when validated against with results from the Lux-Lung 3 trial (Griebsch et al., BMJ Open 2014; 4(10)), in which disease progression was associated with a utility decrement of -0.061. If this decrement is subtracted from the progression-free disease utility from Shor et al., the progressed disease values are 0.754 (PD1) and 0.693 (PD2), which are very close to the utilities assigned to these states based on the range presented in Shor et al.

Three alternative sets of utility values from other sources were included in sensitivity analysis and had a moderate impact on the CUA results (see Section 4.7). These values, as well as the base case, are presented in

Table 14 below.

Table 14: Utility values used in sensitivity analysis

Source	Utility weight			Reference/ notes
	Progression-free disease	Progressed disease 1	Progressed disease 2	
Shor et al.	0.815	0.750	0.680	Base case
NICE TA653	0.836	0.797	0.717	NICE TA 653 committee papers p. 31, originally from AURA3 Stable disease mapped to PD1
Swedish Cost-effectiveness study	0.79	0.74	0.47	Nilsson et al., J Med Econ, 2021; 24(1) Osimertinib tx mapped to PFS, 2L tx mapped to PD1, BSC mapped to PD2
Nafees et al.	0.815	0.6532	0.4734	Nafees et al. Health Qual Life Outcomes, 2008; 6(84) PFS from Shor et al. used for PFS since Nafees only included those on 2L tx, stable disease mapped to PD1

BSC – best supportive care, TA – technology appraisal, tx – treatment, PD – Progressed disease

The NICE utility values were originally sourced from trial evidence (AURA3). Though trial results are considered a promising source of utility values, the utility in PFS was higher than the average in the New Zealand population 64-75 age group (Janssen, et al. Eur J Health Econ 20, 2019; 205–216) (the FLAURA trial average age was 63.0 years – ClinicalTrials.gov NCT02296125). This was considered implausible in a population receiving treatment for metastatic NSCLC.

The study by Nilsson was not used in the base case since utility values for people on specific treatments, rather than in specific disease states, were used as a proxy for health state utilities. However, this was considered a potentially useful scenario analysis, in case treatment-specific utilities in some way better captured HRQOL with treatments, relative to utilities specific to disease states.

Finally, though it was considered a low estimate relative to others, the scenario analysis which the supplier proposed including utilities from Nafees et al. was retained since this was considered a fair representation of a low plausible estimate of utilities in progressed disease states.

4.5 Costs

4.5.1 Pharmaceutical Cost

Osimertinib

The net price of a pack containing 30 osimertinib tablets is [redacted] (list price [redacted]), as per the offer in December 2019 (A1355981). The net price per tablet is [redacted], so with daily dosing, the cost per weekly model cycle is [redacted] (7 * [redacted]).

First generation TKIs

The price (list, as no net price was provided) of a pack containing 30 erlotinib tablets is $569.70 (Pharmaceutical schedule). The price per tablet is $18.99, so with daily dosing the cost per weekly model cycle is $132.93.

The net price of a pack containing 30 gefitinib tablets is [redacted] (list price $918), as per the 2021 contract with the supplier (A1553818). The net price per tablet is [redacted], so with daily dosing, the cost per weekly model cycle is [redacted].

As noted earlier, Pharmac dispensing data (Pharmac Qlik: Patients -> Erlotinib or gefitinib 2018/19 to 2020/21) indicates that approximately 63% of people with EGFRm positive NSCLC receive erlotinib as 1L treatment, with the remaining ~37% receiving gefitinib. Applying this weighting to the cost of each TKI results in a weighted average cost of 1st gen. TKI treatment of [redacted] per week.

Chemotherapy & Docetaxel

The chemotherapy and docetaxel regimens are detailed in Table 15 below. Carboplatin with pemetrexed and cisplatin with pemetrexed are the two platinum-based chemotherapy regimens used in the NZ clinical setting and the AURA3 trial. Both regimens are examples of platinum-doublet chemotherapy.

Table 15: Chemotherapy regimens

Regimen	Dose	Source
Carboplatin & pemetrexed	Carboplatin 5 AUC (with a glomerular filtration rate (GFR) of 90 this comes to 575mg) and pemetrexed 500mg/m^2 every 3 weeks for 4-6 cycles. The pemetrexed component is continued until disease progression in the maintenance phase.	EViQ Carboplatin & pemetrexed, AURA3 GFR calculations from previous analysis (A1411257)
Cisplatin & pemetrexed	Cisplatin 75mg/m^2 & pemetrexed 500mg/m^2 every 3 weeks for 4-6 cycles. The pemetrexed component is continued until disease progression in maintenance phase.	EviQ Cisplatin & pemetrexed, AURA3
Docetaxel	75mg/m^2 every 3 weeks for 4 cycles	EviQ Docetaxel

The cost per chemotherapy agent, assuming a mean body surface area (BSA) of 1.92m^2 (CUA cost spreadsheet – A1034373) for those with dosing based on BSC, is presented in Table 16.

Table 16: Pharmaceutical cost of each chemotherapy agent

Agent	ECP price per mg	Dose (mg)	Cost per dose	Source of price
Carboplatin	$0.10	575	$57.50	Pharmaceutical Schedule – 1mg Docetaxel inj for ECP
Cisplatin	$0.31	144	$44.64	Pharmaceutical Schedule – 1mg Cisplatin inj for ECP
Pemetrexed	$0.55	960	$528.00	Pharmaceutical Schedule – 1mg pemetrexed inj for ECP
Docetaxel	$0.65	144	$93.60	Pharmaceutical Schedule – 1mg Docetaxel inj for ECP

It is not known what proportion of people would receive carboplatin versus cisplatin with the permetrexed, and this was not reported in the AURA3 trial. It has been estimated that 72% of people would receive carboplatin and 28% would receive cisplatin, based on the split from KEYNOTE 189 (Gandhi et al., New Engl J Med, 2018; 378:2078-92. Figure S2), a trial comparing pembrolizumab and chemotherapy to chemotherapy alone in people with NSCLC without EGFR mutations. Pharmac is not aware of any reason this regimen would differ for the EGFRm positive population, and when tested in the sensitivity analysis, the split does not impact model results.

Table 17 below shows the estimated cost in initial and maintenance phases for platinum-based chemotherapy and docetaxel. The initial phase is assumed to last 5 cycles, the mid-point of the 4-6 cycles specified by EviQ.

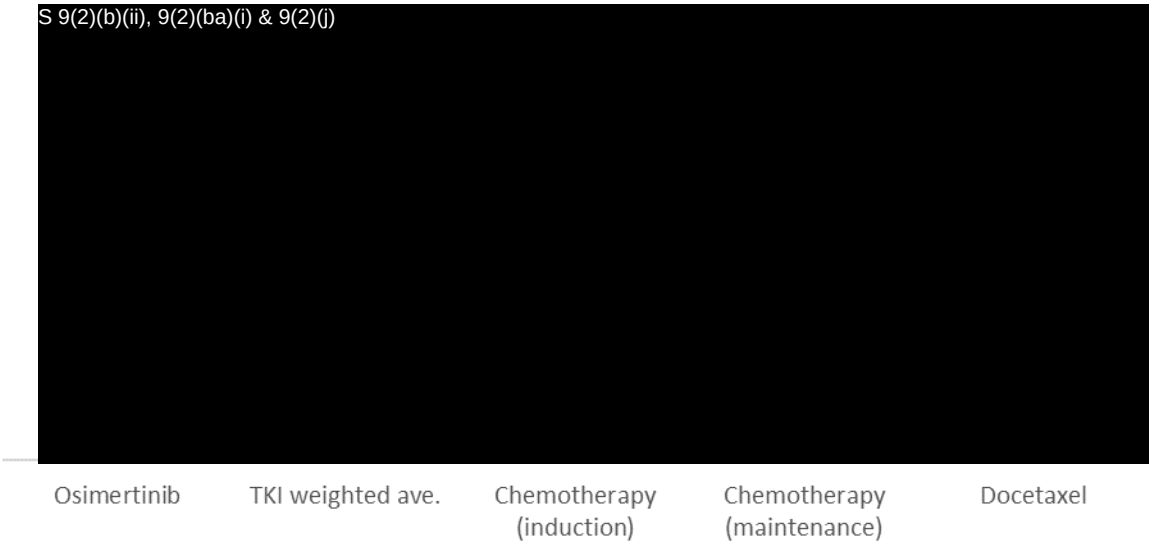
Table 17: Weekly Pharmaceutical cost of chemotherapy and docetaxel

Regimen	Pharmaceutical cost per week	Notes
Platinum-based chemotherapy		
Initial phase (5 cycles)	$194	(72% * $57.50 + 28% * $44.64 + $528) / 3 weeks
Maintenance phase	$176	$528 / 3 weeks
Docetaxel		
Four cycles	$31	$93.60 / 3 weeks

Pharmaceutical cost summary

The weekly pharmaceutical costs for each treatment are outlined in Figure 18 below. The figure illustrates the high pharmaceutical cost of osimertinib compared to current treatments.

Figure 18: Weekly pharmaceutical cost



4.5.2 Pharmacy Margin

Pharmacy margin costs, which compensate pharmacies for procuring and stockpiling pharmaceuticals, are estimated based on the Pharmac Cost and Resource Manual, to be 4% of the list price for pharmaceuticals dispensed in the community (for pharmaceuticals with a pack price > $150): osimertinib, gefitinib and erlotinib.

- The list price for osimertinib is S 9(2)(b)(ii), 9(2) per pack, which implies a cost of S 9(2)(b)(ii), 9(2) per cycle. 4% of this amount results in a pharmacy margin of S 9(2)(b)(ii), 9(2) per cycle.
- The weighted average list price for 1st gen. TKIs is $698 per pack, which implies a cost of $162.87 per cycle. 4% of this amount results in a pharmacy margin of $6.51 per cycle.

4.5.3 Administration Costs

Administration costs associated with chemotherapy and docetaxel were estimated. Osimertinib and 1st gen. TKIs do not incur administration costs since they are administered orally. Table 18 below outlines the infusion duration for each regimen, which is required to estimate the administration costs.

Table 18: Infusion duration

Regimen	Infusion duration (hours)	Source
Carboplatin & pemetrexed (initial phase)	2.00	EviQ Carboplatin & pemetrexed
Cisplatin & pemetrexed (initial phase)	4.00	EviQ Cisplatin & pemetrexed
Chemotherapy weighted average (initial phase)	2.56	2 * 72% + 4 * 28%
Chemotherapy maintenance phase	0.50	EVIQ Pemetrexed
Docetaxel	1.50	EviQ Docetaxel

Table 19 outlines the per-unit cost inputs used to estimate the administration costs associated with chemotherapy and docetaxel. All unit costs are sourced from the Pharmac CUA cost spreadsheet (A1034373).

Table 19: Unit costs associated with administration of pharmaceuticals

Resource	Cost	Unit
Pharmacist (compounding)	$13.75	Per infusion (15 minutes of time)
Nurse	$55.00	Per hour
Outpatient bed	$65.00	Per hour
Specialist	$35.00	Per infusion (15 minutes of time)

The weekly administration costs estimated using the information from the two tables above are outlined in Table 20. The costs have been smoothed across weeks even though they occur three-weekly.

Table 20: Weekly administration costs

Regimen	Cost	Notes
Chemotherapy – Initial phase	$118.65	(2.56 * ($55 + $65) + $13.75 + $35) / 3 weeks
Chemotherapy – Maintenance phase	$36.25	(0.5 * ($55 + $65) + $13.75 + $35) / 3 weeks
Docetaxel	$76.25	(1.5 * ($55 + $65) + $13.75 + $35) / 3 weeks

4.5.4 Monitoring costs

Monitoring costs have been estimated based on the assumption that people with EGFRm positive NSCLC would require one chest computerized tomography (CT) scan and an oncologist visit every 12 weeks. These assumptions are in line with previous metastatic NSCLC modelling in TAR 436 (A1461122). The monitoring costs included in all health states of both models (other than dead) are presented in Table 21.

Table 21: Monitoring costs

Item	Cost per unit	Cost per week	Source/notes
Chest CT scan	$362	$30.18	CUA cost spreadsheet, medical oncology subsequent attendance / 12 weeks
Oncologist visit	$769	$64.08	CUA cost spreadsheet, CT chest scan / 12 weeks
Total monitoring costs	**-**	**$94.26**	$30.18 + $64.08

4.5.5 Hospitalisation costs

Health sector utilisation data was sourced from the PIvoTAL study (Lee et al., BMC Health Services Research, 2018: 18:147). The study retrospectively observed health service utilisation among patients with advanced or metastatic NSCLC across nine countries. The study included 1,440 patients, of whom 208 were from Australia, and 31 of these people had EGFRm or ALK (another, less common mutation) positive disease. The Australian cohort was previously considered to be broadly representative of resource utilisation in New Zealand (CTAC record April 2022), and provides sub-group analysis for the EGFRm positive population by treatment line. The key results from the Australian cohort were:

- In the overall cohort, the number of hospitalisations per 100 patient weeks was 4.83 in the 1L setting and 3.63 in the 2L setting. These rates are tested in sensitivity analysis

- In the 1L setting, there were 35 hospitalisations among 31 people who were EGFRm positive, and 177 hospitalisations among the 95 without a mutation, corresponding to a hospitalisation ratio (EGFRm : No mutation) of 0.61. In other words, people with an EGFR mutation would be expected to have 0.61 hospitalisations for every hospitalisation in the 'no mutation' group.
- In the 2L setting, there were 20 hospitalisations among 22 people who were EGFRm positive, and 49 hospitalisations among the 66 without a mutation, corresponding to a hospitalisation ratio of 1.22. In other words, people with an EGFR mutation would be expected to have 1.22 hospitalisations for every hospitalisation in the 'no mutation' group. People with EGFRm mutations tend to be healthier than those without, so this result is unexpected and may be due to small numbers.
- Due to the unexpected 2L result, a weighted average hospitalisation ratio across 1L and 2L was estimated to be 0.86, which was applied to the number of hospitalisations per 100 patient weeks in the 2L cohort to estimate the number of hospitalisations per 100 patient weeks in the EGFRm positive subgroup.
- The equations below illustrate the estimation of hospitalisations per 100 weeks in both settings:

$$1L\ hospitalisations\ per\ 100\ weeks = 4.83 * 0.61 = 2.93$$

$$2L\ hospitalisations\ per\ 100\ weeks = 3.63 * 0.86 = 3.12$$

The average cost per hospitalisation was estimated by multiplying the cost of each relevant diagnosis related group (DRG) code included in the E71 DRG by the proportion of total discharges coded E71A, B or C with each code. The average cost of an NSCLC hospitalisation was consequently estimated to be $5,359. This calculation is presented in Table 22 below.

Table 22: Weighted average cost of a NSCLC hospitalisation

DRG cost code	Average cost*	Discharges**	Discharges as proportion of total
E71A Respiratory Neoplasms W Catastrophic CC	$9,904	715	20.4%
E71B Respiratory Neoplasms W/O Catastrophic CC	$5,556	1720	49.1%
E71C "Respiratory Neoplasms, Sameday"	$2,004	1070	30.5%
Weighted average cost of NSCLC hospitalisation			**$5,359**

*WIESNZ21 cost weights; Pharmac CUA cost spreadsheet

**Ministry of Health 2020/21 hospitalisation data from National Minimum Dataset, sourced on Qlik database

The average cost per hospitalisation was then multiplied by the estimated number of hospitalisations per 100 weeks derived from Lee et al.:

- 1L: 2.93 * $5,359 = $15,684
- 2L: 3.12 * $5,359 = $16,735

Finally, the costs per 100 weeks were divided by 100 to get a weekly cost, which aligns to the model cycle length. For 1L, the weekly cost is $157, while for 2L it is $167. These costs were then applied each cycle, to all living patients in both the 1L and 2L models, regardless of health state. The one exception was people receiving docetaxel – these costs were

doubled to reflect the high toxicity of docetaxel, which was an arbitrary assumption but is not impactful for model results.

4.5.6 T790M testing costs

Testing for the EGFR mutation is already performed at diagnosis of metastatic NSCLC. However, if osimertinib were funded 2L, additional testing for the T790 mutation would be required to determine eligibility. Correspondence with one of the testing providers indicates that the cost per test is approximately S 9(2)(b)(ii) (A1647300). This cost is applied as a one-off cost in the 2L model. It is acknowledged that the cost may differ substantially between providers, but testing in sensitivity analysis found this cost to be immaterial to model results.

4.6 Cost-Effectiveness Results

1L

In the 1L setting, the incremental cost is estimated to be S 9(2)(b)(ii), 9(2)(ba)(i) & with an incremental QALY gain of 0.82. The estimated cost-effectiveness is therefore S 9(2) QALYs per $1million (cost per QALY of S 9(2)(b)(ii), 9(2)(ba)(i) &). The results are shown in Table 23.

Table 23. 1L Cost-Effectiveness Results

	Osimertinib	Status quo	Incremental
QALYs	2.65	1.83	**0.82**
Cost	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)		
QALYs per $1m			S

The cost-effectiveness of funding osimertinib is likely to be low. The cost utility is driven by:

- The high pharmaceutical cost of osimertinib relative to comparator treatments. Osimertinib costs S 9(2)(b) per week, while a weighted average of the first gen. TKIs costs S 9(2) per week – representing S 9(2)(b)(ii), 9 of the osimertinib pharmaceutical cost
- A key benefit of osimertinib is that people live longer while receiving it, which also means that people incur higher costs of regular health service use, for hospitalisations and monitoring. The higher health sector costs reduce the cost utility
- Significant QALY gain (health benefit) from treatment in terms of longer PFS and OS

2L

In the 2L setting, the incremental cost is estimated to be S 9(2)(b) with a QALY gain of 0.83. The estimated cost-effectiveness is therefore S QALYs per $1million (cost per QALY of S 9(2)(b)(ii), 9(2)(ba)(i) &). This is shown in Table 24.

Table 24. 2L Cost-Effectiveness Results

	Osimertinib	Status quo	Incremental
QALYs	1.92	1.09	**0.83**
Cost	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)		
QALYs per $1m			S

The cost-effectiveness of funding osimertinib is likely to be low. The cost utility is driven by:

- The high pharmaceutical cost of osimertinib relative to comparator treatments. Osimertinib costs S 9(2)(b) per week, while platinum-based chemotherapy costs $257

per week, including administration costs – representing S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2) of the osimertininb pharmaceutical cos

- A key benefit of osimertinib is that people live longer while receiving it, which also means that people incur higher costs of regular health service use, for hospitalisations and monitoring. The higher health sector costs reduce the cost utility
- Significant QALY gain (health benefit) from treatment in terms of longer PFS and OS. The incremental QALY gain in the 2L setting is marginally greater than in the 1L setting, since as a 2L treatment osimertinib adds another effective treatment line, while in the 1L setting it displaces a reasonably effective current treatment.

4.7 Sensitivity Analysis

One-way Sensitivity Analysis

Sensitivity analysis was performed to test the impact of various assumptions. The sensitivity analysis results are presented in Table 25 (1L) and Table 26 (2L). Rows shaded in light orange are included to test model robustness (e.g. impact of discount rates) or for commercial purposes only, and are not included in the likely range. Rows shaded in purple indicate the lower and upper bounds that define the likely CUA range.

Table 25. Sensitivity Analysis -1L

Scenario	Base case value	Sensitivity value	Incremental costs	Incremental QALYs	ICER	QALYs per $m
Base case			S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	**0.82**	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
50% of people using 1st gen. TKIs receive erlotinib, 50% gefitinib	63% erlotinib: 37% gefitinib	50%:50%		0.82		
Alternative hospitalisation rates from Lee et al. study	EGFRm-specific rates	Rates from overall NSCLC cohort		0.82		
Additional hospitalisation costs applied to all treatments other than osimertinib to account for lower AEs on osimertinib	Same hospitalisation costs across treatments	Hospitalisation costs multiplied by an additional 10%		0.82		
40% of people receive chemotherapy as 2L treatment	60%	40%		0.82		
80% of people receive chemotherapy as 2L treatment	60%	80%		0.82		
10% of people receive docetaxel as 3L treatment	30%	10%		0.82		
50% of people receive docetaxel as 3L treatment	30%	50%		0.82		
Higher (+1 SE applied to HR and % change applied) rate of progression on osimertinib	PFS monthly prob. of 1.19% and 4.59%	PFS monthly prob. of 1.32% and 5.08%		0.80		
Lower (-1 SE applied to HR and % change applied) rate of progression on osimertinib	PFS monthly prob. of 1.19% and 4.59%	PFS monthly prob. of 1.06% and 4.10%		0.84		

Scenario	Base case value	Sensitivity value	Incremental costs	Incremental QALYs	ICER	QALYs per $m
Higher (+1 SE applied to HR and % change applied) rate of death on osimertinib	OS monthly prob. of 0.70%, 1.59% and 2.96%	OS monthly prob. of 0.78%, 1.78% and 3.32%	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	0.645	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
Lower (-1 SE applied to HR and % change applied) rate of death on osimertinib	OS monthly prob. of 0.70%, 1.59% and 2.96%	OS monthly prob. of 0.62%, 1.41% and 2.63%		1.018		
The rate of progression for docetaxel is doubled	PFS monthly prob. of 9.2% and 28.0%	PFS monthly prob. of 17.6% and 48.2%		0.82		
Utility values from NICE TA653 used	PFS: 0.815, PD1: 0.75, PD2 0.68	PFS: 0.836, PD1: 0.797, PD2 0.717		0.843		
Utility values from Nilsson et al. study	PFS: 0.815, PD1: 0.75, PD2 0.68	PFS: 0.79, PD1: 0.74, PD2 0.47		0.759		
Utility values from Nafees et al. study	PFS: 0.815, PD1: 0.75, PD2 0.68	PFS: 0.815, PD1: 0.653, PD2 0.473		0.786		
Price of pharmaceutical falls 25%	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)			0.82		
Discount rate (low)	3.5%	0%		0.95		
Discount rate (high)	3.5%	5%		0.773		

SE – standard error

Table 26: Sensitivity Analysis – 2L

Scenario	Base case value	Sensitivity value	Incremental costs	Incremental QALYs	ICER	QALYs per $m
Base case			S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	**0.83**	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
Alternative hospitalisation rates from Lee et al. study	EGFRm-specific rates	Rates from overall NSCLC cohort		0.864		
Additional hospitalisation rates applied to all treatments other than osimertinib to account for lower AEs on osimertinib	Same rates across treatments	Additional 10 percentage points for other treatments		0.864		
T790M test cost doubled	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)			0.864		

Scenario	Base case value	Sensitivity value	Incremental costs	Incremental QALYs	ICER	QALYs per $m
T790M test cost halved	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)		S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	0.864	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
40% of people receive chemotherapy as 2L treatment	60%	40%		0.871		
80% of people receive chemotherapy as 2L treatment	60%	80%		0.857		
10% of people receive docetaxel as 3L treatment	30%	10%		0.864		
50% of people receive docetaxel as 3L treatment	30%	50%		0.864		
Higher (+1 SE applied to HR and % change applied) rate of progression on osimertinib	PFS monthly prob. of 3,82% and 8.97%	PFS monthly prob. of 4.32% and 10.11%		0.82		
Lower (-1 SE applied to HR and % change applied) rate of progression on osimertinib	PFS monthly prob. of 3,82% and 8.97%	PFS monthly prob. of 3.32% and 7.82%		0.84		
Higher (+1 SE applied to HR and percentage change applied) rate of death on osimertinib	OS monthly prob. of 1.49% and 3.63%	OS monthly prob. of 1.69% and 4.12%		0.664		
Lower (-1 SE applied to HR and percentage change applied) rate of death on osimertinib	OS monthly prob. of 1.49% and 3.63%	OS monthly prob. of 1.30% and 3.18%		1.017		
The rate of progression for docetaxel is doubled	PFS monthly prob. Of 9.2% and 23.4%	PFS monthly prob. Of 17.6% and 41.3%		0.864		
Utility values from NICE TA653 used	PD1: 0.75, PD2 0.68	PD1: 0.797, PD2 0.717		0.877		
Utility values from Nilsson et al. study	PD1: 0.75, PD2 0.68	PD1: 0.74, PD2 0.47		0.743		
Utility values from Nafees et al. study	PFS: 0.815, PD1: 0.75, PD2 0.68	PFS: 0.815, PD1: 0.653, PD2 0.473		0.677		
Crossover-adjusted OS from AURA3 used to estimate probability of death on chemotherapy*	Monthly prob. Of death: 1.9% & 5.9%	Monthly prob. Of death: 2.8% & 4.9%		0.627		
Price of pharmaceutical falls 25%	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)			0.864		

Scenario	Base case value	Sensitivity value	Incremental costs	Incremental QALYs	ICER	QALYs per $m
Discount rate (low)	3.5%	0%	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	0.987	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
Discount rate (high)	3.5%	5%		0.819		

** The crossover-adjusted OS from AURA3 was not used as the base case due to the uncertainty around the estimate. The crossover-adjusted hazard ratio of death was 0.54 with a 95% CI range of 0.18-1.60*

The overall cohort included those with and without T790M mutations. It was tested since the number at risk in the T790M positive group was low, so the wider group might reduce the risk of inaccurate OS estimates due to small sample size.

4.8 Summary of Overall Cost-Effectiveness

As outlined above, the base-case cost utility is S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9 Taking into account the results of the sensitivity analysis, the likely range is estimated to be S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j). This range is informed by:

- **1L**: The upper bound reflects higher hospitalisation costs, while the lower bound reflects a higher rate of death on osimertinib treatment.
- **2L**: The upper bound reflects a lower rate of death on osimertinib treatment, while the lower bound reflects the crossover-adjusted OS from AURA3 used to estimate the probability of death for those receiving chemotherapy

In general, the CUA results are not sensitive to changes in model parameters, mainly due to the high pharmaceutical cost of osimertinib relative to comparator treatments. If a lower S 9 (2) price is received, the model results would be more sensitive to model parameters and may need to be revisited.

5. Budget Impact Analysis

5.1 Summary of Budget Impact

The 5-year net present value (NPV) to the Combined Pharmaceutical Budget (CPB) of funding osimertinib 1L is estimated to be S 9(2)(b) (ii), with a cost of the first 12 months of S 9(2)(b) (ii). In the 2L setting, the 5-year NPV is estimated to be S 9(2)(b) (ii), with a cost of the first 12 months of S 9(2)(b) (ii).

The 5-year NPV to the rest of the health system is estimated to be S 9(2)(b) (ii) (1L) and S 9(2)(b) (ii) (2L), meaning the overall cost is estimated to be S 9(2)(b)(ii), 9(2)(ba)(i) & 9 (2)(i), respectively. All costs are discounted at an annual rate of 8%.

5.2 Patient Numbers

Eligible people: 1L

The number of people with each type of NSCLC has been estimated previously in TAR 436 (A1461122) and TAR 436A (A1602092), and has been validated by CTAC (CTAC record April 2022). The assumptions used to arrive at the number of eligible people are presented in Table 27. Patient number estimates assume population growth of 1% per annum.

Table 27: People eligible for treatment – 1L

	Assumption	Estimate	Source/rationale
A	Number of people diagnosed with NSCLC, 2015-18	6,023	Lung Cancer Quality improvement report. Te Aho Te Kahu, 2021. p8
B	People with newly diagnosed NSCLC per year	1,506	A / 4 (2015-18 encompasses 4 years)
C	Proportion with locally advanced or metastatic disease at diagnosis	83.50%	Lawrenson et al., NZMJ 2018; 131:1479
D	People with NSCLC, metastatic disease	1,257	B x C
E	People diagnosed with Stage 1-2 disease (as above - new patients less people with metastatic disease)	248	B - D
F	Proportion progressing to stage 3-4	42%	Sugimura et al., 2007 (445 / 1,073 had disease recurrence)
G	Number progressing to Stage 3-4	104	E x F
H	Proportion with EGFR mutation	20%	Aye et al., 2020
I	**Total eligible people with EGFR mutation in first year of listing**	**272**	**(D + G) * H**

Eligible people: 2L

In 2020 and 2021, an average of 83 people discontinued treatment on erlotinib or gefitinib (Pharmac Qlik Operational Summary of patients by chemical). CTAC estimated that there would also be a prevalent pool of 75 people who have already progressed on a first generation TKI and would proceed to a biopsy if osimertinib were made available.

Most people (95% according to Chu et al., Curr Oncol, 2020; 27(1): 27-33) would be able to undergo a successful biopsy (multiple biopsies are feasible if the initial biopsy is inconclusive given the significant difference between PFS and OS), and approximately 50% would test positive for the T790M mutation (CTAC Record April 2021, para 7.31, Chu et al. 2020). This evidence suggests 75 people would be in the 2L eligible population:

- 39 eligible people in the incident population (83 * 95% * 50%)
- 36 eligible people in the prevalent population (75 * 95% * 50%)

Uptake

From 2019-21, there were an average of 115 people beginning treatment with a first generation TKI (erlotinib or gefitnib), which implies a current uptake of 42.1% (115 divided by 272, see Table 27) (Pharmac Qlik Operational Summary of patients by chemical (calendar year). This rate has been applied in the 1L setting, whereas in the 2L setting it has been assumed that uptake would be 100% among those who test positive for the T790M mutation since they have already been receiving treatment. It is noted that this may be an over-estimate, given that people can experience treatment fatigue as they consider initiating later lines of treatment, though without evidence to inform a lower rate, 100% was assumed conservatively.

The uptake and resulting number of treatment initiators is presented in Table 28. Note that the number of eligible people increases over time in line with forecast population growth.

Table 28: Uptake & number of people initiating treatment

Year	1	2	3	4	5
1L					
Number of people eligible	275	278	281	283	286
Uptake rate	42.1%	42.1%	42.1%	42.1%	42.1%
Number initiating treatment	**116**	**117**	**118**	**119**	**121**
2L					
Number of people eligible	76	40	41	41	41
Uptake rate	100%	100%	100%	100%	100%
Number initiating treatment	**76**	**40**	**41**	**41**	**41**

5.3 Net Budget Impact

The net impact to the CPB over 5 years is outlined in Table 29 below.

Table 29. Net Budget Impact to the Pharmaceutical Budget (CPB)

Year	1	2	3	4	5	5-year NPV
1L						
Osimertinib	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Status Quo						
Incremental costs						
2L						
Osimertinib	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Status Quo						
Incremental costs						

5.4 Net Budget Impact to the wider health system

The net budget impact to the wider health system is shown in Table 30 below.

Table 30. Net Budget Impact to wider health system

Year	1	2	3	4	5	5-year NPV
1L						
Osimertinib	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Status Quo	$1,432,000	$2,465,000	$3,108,000	$3,520,000	$3,791,000	
Incremental costs	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
2L						
Osimertinib	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Status Quo	$303,000	$442,000	$505,000	$535,000	$552,000	
Incremental costs	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

Finally, the overall net costs (pharmaceutical costs and costs to the wider health system) are presented in Table 31.

Table 31. Overall net budget Impact – Incremental costs

Year	1	2	3	4	5	5-year NPV
1L						
CPB	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Wider health system	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Overall	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
2L						
CPB	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Wider health system	$S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Overall	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

5.5 Patient Costs

Osimertinib is dispensed at community pharmacies, so people will incur a $5 prescription fee for each pack. Erlotinib and gefitinib are both dispensed in the community, so 1L listing of osimertinib would not change the costs paid by the individual receiving treatment. If listed 2L however, it would likely save people time and travel costs since they will no longer need to receive chemotherapy infusions in a hospital setting. The groups who would benefit most from this change are those who live rurally and those in low socioeconomic groups who are less able to afford taking time off work to receive treatment.