PHARMAC
TE PĀTAKA WHAIORANGA

PHARMACEUTICAL SCHEDULE APPLICATION

To: Cancer Advisory Committee

From: Funding Application Advisor

Date: April 2022

Osimertinib for the adjuvant treatment of EGFR positive non-small cell lung cancer following tumour resection [P-001690]

SUMMARY OF PHARMACEUTICAL			
Brand Name	Tagrisso	**Chemical Name**	Osimertinib
Indications	Adjuvant treatment after tumour resection in adult patients with non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations	**Presentation**	40 mg and 80 mg tablets
Therapeutic Group	Oncology and Immunosuppressants	**Dosage**	80 mg once a day
Supplier	AstraZeneca	**Application Date**	May 2021
MOH Restrictions	Prescription medicine	**Proposal type**	New listing
Current Subsidy	NA	**Proposed Restriction**	Special Authority
Proposed Subsidy	Gross $9310 per 30 tablets (equal to net)	**Approved by Medsafe for this indication**	Yes
Market Data	Year 1	Year 2	Year 3
Number of new Patients†	10	12	14
Net Cost to Schedule†	$S 9(2) (b)(ii)	$S 9(2) (b)(ii)	$S 9(2) (b)(ii)
Net Cost to DHBs* (5-year NPV, 8%)	$S 9(2) (b)(ii)		

DHBs, District health board; MOH, Ministry of Health; NPV, Net Present Value.
†Supplier estimate.
*Combining the cost to the Schedule and cost to DHBs.

QUESTIONS TO THE COMMITTEE

Note to members: These questions have been identified by Pharmac staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.

Need

1. Considering the currently available treatments for EGFRm positive non-small cell lung cancer (NSCLC) following tumour resection, is there an unmet health need?

    1.1. How severe is this health need of patients with EGFRm positive non-small cell lung cancer following tumour resection? (Please describe the health need of a person with a condition over their lifetime on current treatment).

    1.2. What is the strength and quality of evidence for this health need?

2. What is the Committee's view of the patient number estimates by the applicant and Pharmac staff?

3. What are the health needs of families and whānau of people with stage IB to IIIa/resectable NSCLC (including long-term effects) or of wider society? How severe are these needs?

    3.1. What is the strength and quality of evidence for these needs?

4. Does early-stage NSCLC disproportionally affect:

    - Māori?
    - Pacific people?
    - Other groups already experiencing health disparities relative to the wider New Zealand population (eg. NZ Dep 9-10 deprivation, refugees/asylum seekers)?

    4.1. What is the strength and quality of evidence that supports any disproportionate effect of early stage NSCLC on these patient populations?

    4.2. Is the proportion of these groups in regard to this diagnostic stage disproportionate to what it should be (considering the association between patients with NSCLC presenting at a later diagnostic stage and the access inequities these groups face)?

Health benefit

5. Does osimertinib provide any additional health benefit or create any additional risks compared with other funded treatment options? If so, what benefits or risks are different from alternative treatments?

6. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from osimertinib?

7. Would osimertinib produce a health benefit for family, whānau or wider society, additional to the health benefits for people with EGFRm positive NSCLC following tumour resection? If so how, and what is the strength and quality of evidence for this benefit?

8. What's the Committee's view of the current treatment paradigm for stage IB to IIIa/resectable NSCLC in New Zealand (**Figure 1**)?

9. What is the Committee's view of the proposed treatment paradigm (**Figure 1**)?

   9.1. Noting that osimertinib has been considered for first- and second-line treatment of metastatic EGFRm NSCLC, and gefitinib and erlotinib are also tyrosine kinase inhibitors funded for metastatic EGFRm NSCLC, does the Committee consider that funding of osimertinib in the adjuvant setting would impact the use of these agents?

10. If osimertinib were to be funded, are there any consequences to the health system that have not been noted in the application or in this paper?

11. Noting the pivotal data from the ADAURA trial (Wu et al. N Engl J Med. 2020;282:1711-23), does the Committee consider a maximum of three years to be an appropriate treatment duration for adjuvant treatment with osimertinib?

    11.1. If not, why not?

12. Is there any evidence to suggest that the disease-free survival benefit seen in the ADAURA trial will translate into a meaningful overall survival benefit?

13. Is NICE's assumption of a "cure" if patients do not progress 8 years after treatment initiation reasonable?

Suitability

14. Are there any non-clinical features of osimertinib (eg formulation, size, shape) that may impact on use, either by the patient, by family, or by healthcare workers, that have not been considered in the application?

Costs and savings

15. Does the information in the PICO table (Table 4) accurately reflect the intended population, intervention, comparator and outcome, if osimertinib were to be funded for adjuvant treatment following resection of EGFRm positive NSCLC? If not, how should this be adjusted?

    Do the patient numbers estimated by the supplier seem reasonable? Specifically does the estimate of 44% relating to the proportion of patients who have had surgical resection that are stage IB to IIIA seem accurate?

    What proportion of patients currently receive platinum-based chemotherapy as adjuvant therapy after surgery?

    15.1. Is it reasonable to assume this same proportion of patients would continue to receive adjuvant chemotherapy in combination with osimertinib?

    15.2. If patients have received platinum-based chemotherapy in conjunction with osimertinib as adjuvant therapy, would they continue to receive further platinum-based chemotherapy on progression?

16. Would the use of osimertinib **create** any significant changes in health-sector expenditure other than for direct treatment costs (eg diagnostic testing, nursing costs or treatment of side-effects)?

    16.1. Do the health system resource consumptions outlined in the Cost and Savings section sound reasonable to apply to the NZ NSCLC population?

General

17. Is there any data or information missing from the application, in particular clinical trial data and commentary?

Recommendations

18. Should osimertinib be listed in the Pharmaceutical Schedule?

    - Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.

19. If listing is recommended, what priority rating would you give to this proposal? **[low / medium / high / only if cost-neutral]**?

20. Are the proposed Special Authority criteria appropriate? If not, how should these be amended?

    20.1. Is it necessary to include a performance score in the Special Authority criteria? If so, what should it be?

21. Does the Committee have any recommendations additional to the application?

PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Committee regarding an application from AstraZeneca for the use of osimertinib (Tagrisso) for the adjuvant treatment of EGFRm positive non-small cell lung cancer (NSCLC) following surgical resection.

DISCUSSION

BACKGROUND

Pharmac has not previously received an application for consideration of adjuvant treatment of EGFRm positive NSCLC.

Previous consideration of treatments for EGFRm positive NSCLC

Currently funded treatments:

Two first-generation tyrosine kinase inhibitors (TKIs), erlotinib (Tarceva) and gefitinib (Iressa) are currently funded for the first line treatment of locally advanced or metastatic, unresectable, non-squamous EGFRm positive NSCLC. Both are oral tablet formulations taken once daily. Following progression on erlotinib or gefitinib, patients may receive platinum-based doublet chemotherapy and then after subsequent progression, receive treatment with docetaxel.

Erlotinib and gefitinib are both currently listed on the Pharmaceutical Schedule subject to Special Authority criteria (links to relevant SA criteria):

- Erlotinib
- Gefitinib

Previous consideration of osimertinib

Osimertinib has been previously considered by Pharmac for two indications; first line treatment of patients with locally advanced/metastatic EGFRm NSCLC, and second line treatment of patients with locally advanced/metastatic EGFRm NSCLC. Table 1 below summarises the previous consideration of these applications.

Table 1: Most recent considerations of osimertinib (all currently under assessment; records available in Appendix 1)

Indication	PTAC/Subcommittee recommendations	Justification
First-line treatment of patients with locally advanced or metastatic EGFRm NSCLC	PTAC – August 2020 Cost neutral to current first-line pharmaceuticals in this indication	• 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; and • High quality, randomised-control trial evidence that reported benefit in progression free survival compared with the comparator (gefitinib or erlotinib); and • Uncertain evidence regarding benefit in overall survival compared with the comparator (erlotinib or gefitinib); and • The lack of evidence of superiority of osimertinib to the current two first-line pharmaceuticals for this indication.

	CaTSoP – April 2021 High	• The health need of patients with EGFRm positive NSCLC; and • Evidence supporting an overall survival (OS) benefit with osimertinib compared to first-generation tyrosine kinase inhibitors (TKIs) following long term follow-up, in a comparable patient population.
Second-line treatment of patients with locally advanced or metastatic EGFRm NSCLC	PTAC – 21 August 2020 Deferred	Pending publication and peer-review of the AURA-3 overall survival results
	CaTSoP – April 2021 High (after prior EGFR tyrosine kinase inhibitor (TKI) therapy)	• The health need of patients with EGFR T790M mutation-positive NSCLC; and • Evidence of a progression free survival (PFS) benefit with osimertinib in the second-line for EGFR T790M mutated NSCLC and supporting evidence of an OS benefit from osimertinib second-line in a comparable population, and the suitability of osimertinib compared with systemic chemotherapy.

The discussion papers provided to PTAC in 2020 and CaTSoP in 2021, and subsequent records as they relate to prior consideration of osimertinib for the above indications, are available in Appendix 1.

Need

The health need of patients with EGFRm positive NSCLC was previously well described in the August 2020 PTAC and CaTSoP 2021 discussion papers available in Appendix 1. Epidemiology data and other relevant sections have been updated to align with the most recent data, and information specific for the requested indication.

Description of the disease

NSCLC is grouped into 5 stages – the requested stages for this application are stages IB, II, and IIIA. Tumours in these stages have not yet metastasised to distal organs and are therefore usually resectable.

Stage IB tumours are more than 3 cm but 4 cm or less in size. Stage II NSCLC is divided into 2 subgroups:

- A stage IIA cancer describes a tumour larger than 4 cm but 5 cm or less in size that has not spread to the nearby lymph nodes.
- Stage IIB lung cancer describes a tumour that is 5 cm or less in size that has spread to the lymph nodes within the lung, called the N1 lymph nodes. A stage IIB cancer can also be a tumour more than 5 cm wide that has not spread to the lymph nodes.

With Stage IIIA cancers, the tumour is 5 centimetres or smaller and has spread to lymph nodes on the same side of the chest as the primary tumour.

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 TKI inhibitors in lung cancer.

Epidemiology

In 2019, a total of 2,344 lung cancer registrations were recorded in New Zealand, with an age standardised rate of 27.6 per 100,000 (Ministry of Health, 2021).

Māori are disproportionately impacted by lung cancer, compared with non-Māori: In 2019, the incidence of lung cancer for Māori was 68.4 per 100,000. Lung cancer also develops earlier in Māori compared with non-Māori, incidence rates peaking at age 70-74 years for Māori (730.3 per 100,000) and age 80-84 years for non-Māori (256.9 per 100,000) (Ministry of Health, 2019).

A 2021 study by Aye et al. reported that standardised incidence ratios of EGFRm positive NSCLC were higher for Pacific people, Asian people, and Māori than Europeans; 3.47, 3.35, 2.02, and 1 respectively (PLoS One. 2021;16:e0251357).

Surgery is an available treatment option for patients with early-stage NSCLC. A recent Te Aho report indicated that between 2015 - 2018, 16.7 percent of NSCLC patients overall underwent curative surgical resection in New Zealand, increasing to 17.2 percent of those with NSCLC and a prior pathological diagnosis. (Te o Te Kahu. 2021. Lung Cancer Quality Improvement Monitoring Report 2021).

The health need of the person

Please refer to the documents in Appendix 1 for further information on health need of the patient, family, whānau, and wider society.

The availability and suitability of existing medicines, medical devices and treatments

There are currently no targeted options for adjuvant therapy following resection of EGFRm positive NSCLC. Patients currently receive platinum-based chemotherapy if deemed necessary or appropriate following surgery, followed by docetaxel upon progression (see current treatment paradigm in Figure 1 in the below “Health Benefits” section).

The 2021 Te Aho report indicated that of those diagnosed with NSCLC, systemic anti-cancer therapy was received by 32.0% of Māori patients, 37.7% of Pacific patients, 42.4% of Asian patients, and 27.0% of NZ European/Other patients.

The impact on the Māori health areas of focus and Māori health outcomes

As noted above, Māori experience a substantially higher rate of lung cancer compared with non-Māori. Māori also generally develop lung cancer earlier in life, however, are often diagnosed at more advanced stages than non-Māori, which negatively impacts prognosis. Lung cancer accounts for nearly one third of all Māori cancer deaths (Health Quality and Safety Commission NZ; 2016).

According to the Te Aho report, Māori and Pacific peoples had the lowest curative resection rate overall compared with other ethnic groups (13.4% for Māori, 12.2% for Pacific people, 25.0% for Asian people, and 17.2% for NZ European/Other).

Māori also had the lowest overall survival of all ethnic groups, with 37.7 percent alive one year after diagnosis, 21.6 percent two years after diagnosis and 17.5 percent three years after diagnosis. This was only slightly less than the survival proportion for New Zealand Europeans.

The Te Aho report also references a 2020 publication by Lawrenson et al. (BMC Cancer. 2020;20:109) that reported similar rates of curative treatment for Māori and non-Māori, once they reach diagnosis, which further highlights the systematic barriers along the cancer diagnosis and treatment pathway.

Lung cancer is one of the five Hauora Arotahi – Pharmac Māori Health Areas of Focus.

The impact on Government health priorities

This application aligns with the Government health priority of cancer. Specifically, lung cancer is a focus for Pharmac under the Hauora Arotahi Māori health areas of focus.

Health Benefit

Details of the pharmaceutical under consideration

Clinical Pharmacology and Mechanism of Action

Osimertinib is an orally administered third generation TKI. It is a selective and irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harbouring single (L858R or del746-750) or double (L858R/T790M or del746-750/T790M) mutations.

New Zealand Regulatory Approval

Osimertinib is Medsafe registered for:

- The adjuvant treatment after tumour resection in adult patients with non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) mutations.
- The first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations.
- The treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Recommended Dosage

80 mg taken orally once a day at the same time, without regard to food. If dose reduction is required (based on individual safety and tolerability), 40 mg once a day.

The supplier has noted that osimertinib in the adjuvant setting post resection of EGFRm positive NSCLC should not be used for longer than three years, or in the case of disease progression (as per the clinical trial summarised in Table 3 below).

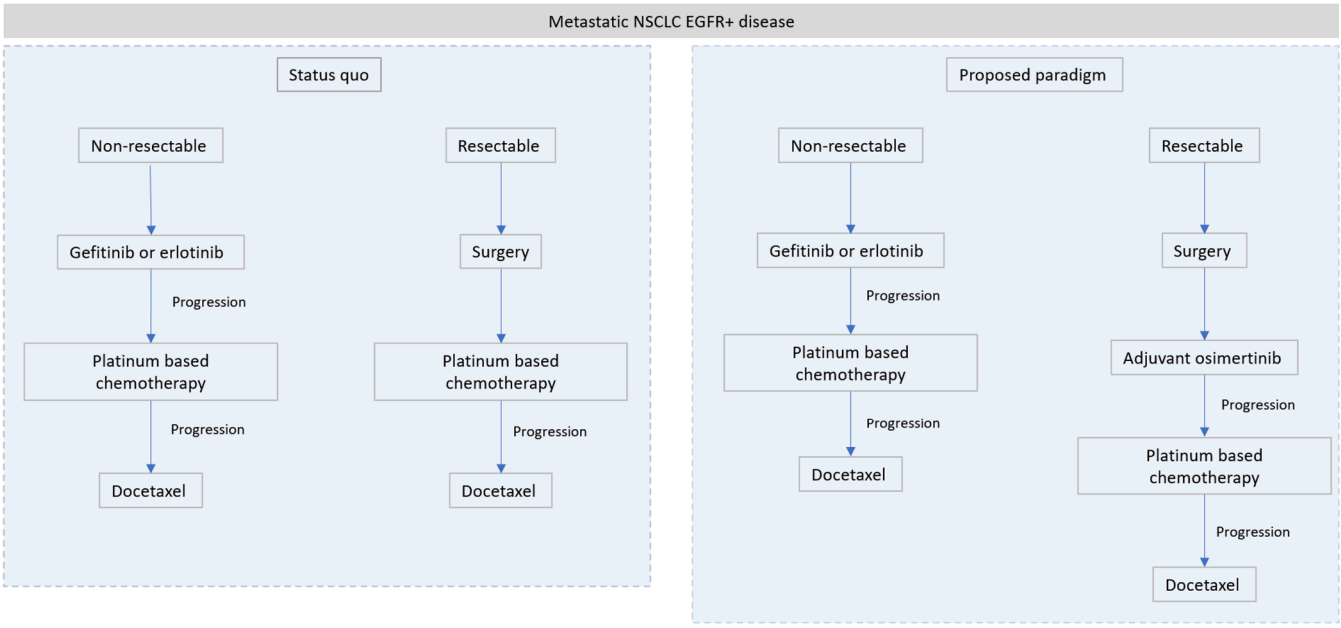
Proposed Treatment Paradigm

The current and proposed treatment paradigms are available in Figure 1 below. Note, the requested line of treatment for this application for osimertinib is the only addition to the treatment paradigm, and previous considerations for osimertinib have not been included.

Members have previously noted that there was sparse evidence to inform what potential benefit patients who received first-line osimertinib might receive from second-line treatment with first-generation TKIs (gefitinib or erlotinib) in the event of disease progression following osimertinib treatment.

Pharmac staff seek the Committee's advice regarding if patients who progress following tumour resection and adjuvant treatment with osimertinib would be eligible for subsequent treatment with gefitinib or erlotinib.

Figure 1: Current and proposed treatment paradigms for EGFRm+ NSCLC in New Zealand



Proposed Special Authority Criteria

Pharmac staff have drafted the below Special Authority criteria based primarily on the eligibility criteria of the pivotal trial for osimertinib in this setting:

OSIMERTINIB
Special Authority for Subsidy – Retail Pharmacy - Specialist
Initial application – (NSCLC – adjuvant following resection) only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Treatment is to be used as an adjuvant therapy following surgical resection of Stage IB to Stage IIIA non-squamous Non-Small Cell Lung Cancer (NSCLC); and
2. There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and
3. Patient has a ECOG Performance status of less than 2; and
4. Patient has not received prior neo-adjuvant treatment with a tyrosine kinase inhibitor; and
5. Patient has not received perioperative or postoperative radiation therapy

Renewal - only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

1. The treatment remains clinically appropriate and the patient is benefitting from treatment; and
2. Radiological assessment (preferably including CT scan) indicates NSCLC has not progressed; and;
3. Treatment with osimertinib to cease upon signs of disease progression; and
4. Total continuous treatment duration must not exceed three years.

International Recommendations

Table 2: International recommendations regarding the funding of osimertinib for the adjuvant treatment of resected EGFRm positive NSCLC

Country (HTA Agency)	Date	Outcome	Reason
Australia (PBAC)	Pharmac staff did not identify any considerations by PBAC regarding osimertinib for the requested indication		
Canada (CADTH - CDEC)	Jan 2022	✓ The CADTH recommended that osimertinib should be reimbursed as adjuvant therapy after tumour resection for the treatment of adult patients with stage IB-IIIA non–small cell lung cancer (NSCLC) whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations only if certain conditions are met.	The ADAURA trial demonstrated that adjuvant treatment with osimertinib resulted in a statistically significant and clinically meaningful prolongation in disease-free survival (DFS) compared to placebo. pERC acknowledged that a DFS benefit of the magnitude observed in the ADAURA trial is likely to be associated with positive impacts such as improvement in patient quality of life by delaying the presentation of advanced or metastatic disease which is associated with substantial morbidity. Although the overall incidence of adverse events (AEs) was higher in patients treated with osimertinib, the toxicities observed were consistent with the known safety profile of osimertinib and pERC considered them manageable for clinicians who have experience with the drug from its use in the metastatic setting.
Scotland (SMC)	Oct 2021	✓ The SMC recommended osimertinib as monotherapy for the adjuvant treatment after complete tumour resection in adult patients with stage IB-IIIA NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions (Ex19del) or exon 21 (L858R) substitution mutations.	Treatment with osimertinib is subject to a three-year clinical stopping rule. In a placebo-controlled phase III study, osimertinib significantly improved disease-free survival (DFS) in patients with completely resected EGFR mutation-positive NSCLC.
England/Wales (NICE)	Jan 2022	✓ The NICE recommended osimertinib for use as adjuvant treatment after complete tumour resection in adults	It is recommended only if: • osimertinib is stopped at 3 years, or earlier if there is disease recurrence or unacceptable toxicity and

Country (HTA Agency)	Date	Outcome	Reason
		with stage 1b to 3a NSCLC whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 (L858R) substitution mutations.	• the company provides osimertinib according to the managed access agreement. The NICE made this recommendation based on the current lack of targeted adjuvant treatments available for NSCLC after complete tumour resection, and the evidence of efficacy of osimertinib as demonstrated in the ADAURA trial.

The health benefits to the person, family, whānau and wider society

Evidence Summary

The supplier has identified one trial that provides the primary evidence for the health benefits of osimertinib for adjuvant treatment after tumour resection in patients with NSCLC whose tumours have EGFR mutations. A summary of this trial is provided in the table below (Table 3). The full text publications are available in Appendix 2.

Table 3: Summary of key evidence for osimertinib for the adjuvant treatment of resected NSCLC with EGFRm

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy & Safety	Citation
ADAURA	Randomised, double-blind, placebo-controlled, phase III trial	At least 18 years of age, with a World Health Organization performance status of 0 or 1; primary nonsquamous NSCLC with postsurgical pathological stage IB, II, or IIIA; and a centrally confirmed EGFR mutation. Note: treatment with preop, post-op or planned radiation not allowed	N=682	Osimertinib 80 mg once daily (n=339) Placebo (n=343) 76% of patients with stage II to IIIA disease 26% of patients with stage IB disease (26%) received adjuvant platinum-based chemotherapy	3 years	**Efficacy** Median follow-up for disease-free survival was 22.1 months in the osimertinib group and 14.9 months in the placebo group. Percentage of patients who were alive and disease-free at 24 months: • Osimertinib group 90% (95% CI 84-93) • Placebo group 44% (95% CI 37-51) • Overall HR for disease recurrence or death 0.17 (99.06% CI 0.11-0.26; P<0.001) Median disease-free survival at 24 months: • Osimertinib: not reached (95% CI 38.8 months to “not calculated”) • Placebo: 19.6 months (95% CI 16.6 to 24.5) Disease recurrence or death: • Osimertinib: 37 of 339 patients (11%) • Placebo: 159 of 343 patients (46%) Patients alive and disease free at 24 months: • Osimertinib: 89% (95% CI 85-92) • Placebo: 52% (95% CI 46-58) • Overall HR for disease recurrence or death, 0.20 (99.12% CI 0.14-0.30; P<0.001) Median disease-free survival at 27.5 months: • Osimertinib: not reached • Placebo: 27.5 months (95% CI 22.0-35.0) Among the patients who **received** adjuvant chemotherapy alive and disease-free at 24 months: • Osimertinib: 89% (95% CI 83-93) • Placebo: 49% (95% CI 41-56) • Overall HR for disease recurrence or death, 0.16 (95% CI 0.10-0.26). Among the patients who **did not receive** adjuvant chemotherapy alive and disease-free at 24 months:	Wu et al. N Engl J Med. 2020;282:1711-23 (Supplement available with submission)

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy & Safety	Citation
						• Osimertinib: 89% (95% CI 81-94) • Placebo: 58% (95% CI 49-67) • Overall HR for disease recurrence or death 0.23 (95% CI 0.13-0.40) At 24 months, 98% of the patients (95% CI 95-99) in the osimertinib group and 85% of the patients (95% CI 80-89) in the placebo group were alive without CNS-related disease (overall HR for CNS disease recurrence or death, 0.18 (95% CI 0.10-0.33). At the data cut-off date, 29 patients in the overall population had died (9 in the osimertinib group and 20 in the placebo group). **Safety** Median duration of total treatment exposure: • Osimertinib group 22.5 months (0-38) • Placebo group 18.7 months (0-36) Any adverse event (AE): • Osimertinib: 329 patients • Placebo: 306 Interstitial lung disease (grouped terms) was reported in 10 patients in the osimertinib group (3%) and in none of the patients in the placebo group. Adverse events of grade 3 or higher were reported in 68 patients (20%) in the osimertinib group and in 46 patients (13%) in the placebo group. Serious adverse events were reported in 54 patients (16%) in the osimertinib group and in 42 patients (12%) in the placebo group (pneumonia most common in both treatment groups with 4 and 5 patients for osimertinib and placebo, respectively)	

The supplier also referenced a quality of life study in their submission, which has since been published (Majem et al. Clin Cancer Res. 2022; Online ahead of print; Appendix 2). Health related quality of life (HRQoL) was measured using the Short Form-36 (SF-36) health survey at baseline, 12, and 24 weeks, then every 24 weeks until recurrence or treatment completion/discontinuation. Baseline physical/mental component summary (PCS/MCS) scores were comparable between osimertinib and placebo (range, 46-47) and maintained to week 96, with no clinically meaningful differences between treatment arms. There were no differences between arms for time-to-deterioration of PCS and MCS; HR, 1.17 (95% CI 0.82-1.67) and HR, 0.98 (95% CI, 0.70-1.39), respectively.

Literature Search

Pharmac staff conducted a PubMed search on 21/03/2022 (search terms: osimertinib AND non-small-cell lung cancer AND resected) and identified no additional publications regarding osimertinib for adjuvant treatment of EGFRm NSCLC following resection that were not identified by the supplier.

Consequences for the health system

As the treatment is administered orally in the community, this would have minimal impact on the administration of treatments in the health care system.

The supplier has noted that trial data indicates that treatment with osimertinib resulted in a significant reduction in disease recurrence – and this was particularly the case for distant recurrence and CNS recurrence. It is stated that most recurrences that occurred with adjuvant osimertinib were loco-regional recurrences, which are associated with better prognosis and less intensive subsequent treatment vs. distant metastases. CNS metastases cause patients and the health system to suffer a significantly higher disease burden, because of seizures, fatigue, speech problems and mobility issues for patients. Reducing CNS metastases is expected to reduce disease burden on the health system.

Suitability

The features of the medicine or medical device that impact on use

Osimertinib is a once daily oral treatment which is easily self-administered, or administered by family, whānau, or caregivers.

Costs and Savings

PICO (Population, Intervention, Comparator, Outcome)

Table **4** below summarises *Pharmac* staff's interpretation of the PICO for osimertinib if it were to be funded in New Zealand for EGFRm positive NSCLC patients as an adjuvant treatment post tumour resection.

This PICO captures key clinical contexts, helping review the proposal and frame any future economic assessment by Pharmac. We seek the Committee's advice on the content in the table below.

Note that the PICO may change as clinical and other features evolve.

Table 4: PICO for Osimertinib if it were to be funded in New Zealand for patients with EGFR mutation NSCLC who have had tumour resection.

Population	Patients with EGFR mutation NSCLC who have had tumour resection.
Intervention	Osimertinib, 80mg (tablet) once per day until disease progression or max duration of 3 years (whichever is earlier). On progression: 1) Platinum based chemotherapy 2) Docetaxel
Comparator(s) (NZ context)	Platinum based chemotherapy On progression 1) Docetaxel
Outcome(s)	Longer disease-free survival (median disease-free survival was 27.5 months for placebo and not reached for Osimertinib). Overall survival is expected to be longer, however data is too immature to draw conclusions from.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

Costs and savings to pharmaceutical expenditure

Cost per patient

The applicant recommends the daily dose to be 80 mg (one, 80 mg tablet). The list price is $9,310 for 1 pack of 30 x 80mg tablets. S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

At this stage Pharmac have considered the list price as part of this BIA based on the ability to proceed with listing of this indication, independent of other funding applications.

The cost per year of treatment per patient is $112,000. The median duration of treatment in the ADAURA study for patients on Osimertinib was 22.5 months (Wu et al, 2020).[1] This results in a cost per patient of $212,000.

Estimated Incremental Total Cost of Listing

The supplier estimates patient numbers ranging from 10-18 patients per year as outlined in the table below. This would create a cost to Pharmac of approximately $2-4 million per year.

Table 5: Supplier estimate of patient numbers

Parameter	Estimate	2022	2023	2024	2025	2026	Source
NZ population		5,173,200	5,222,400	5,271,100	5,319,400	5,367,100	Stats NZ
Rate of incident cases of lung cancer[2]		0.048%	0.048%	0.048%	0.048%	0.048%	
No. of Incident cases lung cancer		2,468	2,491	2514	2537	2560	
NSCLC	70.20%	1,733	1,749	1,765	1,781	1,797	Lung cancer quality improvement report (Te Aho, 2021)
Curative Resection Rate	16.70%	289	292	295	297	300	Lung cancer quality improvement report (Te Aho, 2021)
Stage IB to IIIA and eligible for full resection	44.00%	127	128	130	131	132	Supplier estimate based on Australian data (no reference provided)
EGFRm+	15.50%	20	20	20	20	20	Tin tin et al. Cancer Epidemiol. 2018;57:24-32
New Patients Treated with Osimertinib (proportion)	Varies by year	50%	60%	70%	80%	90%	Supplier assumption
New Patients Treated with osimertinib (number)		**10**	**12**	**14**	**16**	**18**	

Costs and savings to the rest of the health system

Being a patient with NSCLC requires the use of health system services beyond those relating to treatment. Inclusion of these costs such as diagnostics, frequent specialist visits, hospitalisations, supportive care and palliative care in modelling could be important as although the costs may not differ as a result of treatment, the costs associated with survival from treatment are increased.

[1] Note that ADAURA had a stopping criterion at 3 years.
[2] Based on lung cancer incidence rate 2015-2017, MoH Cancer Registry.

Cost Effectiveness (combining the Health Benefits and Costs quadrants)

Lemmon et al. Cost effectiveness analysis

A cost effectiveness analysis of adjuvant osimertinib for patients with resected EGFR-mutant Non-Small Cell Lung Cancer was recently published (Lemmon et al. Oncologist. 2022;oyac021). The following are excerpts from the paper.

> *[Lemmon et al.] constructed a Markov model using post-resection health state transitions with digitized DFS data from the ADAURA trial to compare cost and quality-adjusted life years (QALYs) of 3 years of adjuvant osimertinib versus placebo over a 10-year time horizon. An overall survival (OS) benefit of 5% was assumed. Patients entering the PD state were assumed to be re-treated with osimertinib for up to 2 years for this recurrence based on prior data showing efficacy of this strategy, and based on best estimates of duration of treatment. Costs and utility values were derived from Medicare reimbursement data and literature. The incremental cost-effectiveness ratio for adjuvant osimertinib was $317 119 per QALY-gained versus placebo.*

Lemmon et al. used a cost of $222 196 (USD) per year of Osimertinib treatment, over double the offered list price of a year's treatment in New Zealand ($112,000). This ICER ($317,199) is equivalent to 3 QALYs per $million spent.

NICE Technology appraisal of adjuvant Osimertinib.

NICE adapted a supplier CUA model of osimertinib for adjuvant treatment of EGFR mutation positive non-small-cell lung cancer after complete tumour resection. The model had five health states: disease free, loco-regional recurrence, first-line treatment for distant metastases, second-line treatment for distant metastases, and dead. On progression, patients would be treated with atezolizumab, bevacizumab, carboplatin and paclitaxel, or re-treated with osimertinib. Overall survival gains are based on an assumed "cure" for patients if patients have not progressed five (or eight for second scenario) years after treatment initiation. They concluded that the plausible ICER for osimertinib was in the range of less than £20,000 per QALY gained to more than £30,000 per QALY gained [sic].

APPENDICES

Appendix 1: 2020_08 PTAC discussion paper_ Osimertinib for first line locally advanced or metastatic EGFRm NSCLC

2021_03_CaTSoP discussion paper_ Osimertinib 1L EGFRm NSCLC + 2L T790M

2021-04-21 April CaTSoP record – Osimertinib

2020-08 PTAC record – Osimertinib

Appendix 2: Wu et al. N Engl J Med. 2020;282:1711-23

Majem et al. Clin Cancer Res. 2022; Online ahead of print

THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system

PHARMAC
TE PĀTAKA WHAIORANGA

PHARMACEUTICAL SCHEDULE APPLICATION

To: Pharmacology and Therapeutics Advisory Committee (PTAC)

From: Funding Application Advisor

Date: August 2020

Osimertinib for the first-line treatment of locally advanced or metastatic epidermal growth factor receptor mutation (EGFRm) non-small cell lung cancer (NSCLC)

SUMMARY OF PHARMACEUTICAL			
Brand Name	Tagrisso	**Chemical Name**	Osimertinib
Indications	Adult patients with locally advanced or metastatic EGFRm NSCLC	**Presentation**	40 mg and 80 mg tablets
Therapeutic Group	Oncology and Immunosuppressants	**Dosage**	80 mg once a day
Supplier	AstraZeneca	**Application Date**	December 2019
MOH Restrictions	Prescription medicine	**Proposal type**	New listing
Current Subsidy	NA	**Proposed Restriction**	Special Authority
Proposed Subsidy	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)* per 30 tablets irrespective of strength	**Manufacturer's Surcharge**	Nil
Market Data	Year 1	Year 2	Year 3
Number of Patients†	S 9(2)	S 9(2)	S 9(2)
Net Cost to Schedule†	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
Net Cost to DHBs (5-year NPV, 8%)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)		

DHBs, District health board; MOH, Ministry of Health; NPV, Net Present Value.

*S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) List price proposed as $9,310 per pack for both strengths.

†Supplier estimate.

QUESTIONS TO COMMITTEE

Note to PTAC members: These questions have been identified by PHARMAC staff as being particularly relevant to the application. Please feel free to provide additional information as appropriate.

Need

1. Is there a need for an additional first line EGFR TKI above those currently funded (erlotinib and gefitinib)? Are there any issues with access or availability of current first line EGFR TKIs?
2. How severe is the health need of patients with previously untreated locally advanced or metastatic EGFRm positive NSCLC? Please describe the health need of a person with locally advanced or metastatic EGFRm positive NSCLC condition over their lifetime on current treatment lines.
3. What is the Committee's view of the patient number estimates by the applicant and PHARMAC staff?
4. What are the health needs of families and whānau of people with previously untreated locally advanced or metastatic EGFRm positive NSCLC (including long-term effects) or of wider society? How severe are these needs?
5. Does locally advanced or metastatic EGFRm positive NSCLC disproportionally affect any other groups experiencing health disparities, not mentioned in this paper?
6. What is the strength and quality of evidence in relation to health needs due to this indication?

Health benefit

7. Does osimertinib provide any additional health benefit or create any additional risks compared with other funded treatment options? If so, what benefits or risks are different from alternative treatments?

    7.1. What are the relative health benefits from use of osimertinib in a first-line versus second-line setting?

8. Which patient population would benefit most from osimertinib?
9. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from osimertinib as a first-line treatment?
10. Would first-line osimertinib produce a health benefit for family, whānau or wider society, additional to the health benefits for people with EGFRm positive NSCLC? If so how, and what is the strength and quality of evidence for this benefit?
11. If first-line osimertinib were to be funded, are there any consequences to the health system that have not been noted in the application?

Suitability

12. Are there any non-clinical features of the osimertinib tablet formulation that may impact on use, either by the patient, by family, or by healthcare workers, that have not been considered in the application?

Costs and savings

13. Does the information in the PICO table (Table 3) accurately reflect the intended population, intervention, comparator and outcome, should osimertinib be funded for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC? If not, how should this be adjusted?

    13.1. Would the patient population for first-line osimertinib be expected to be identical to the erlotinib/gefitinib patient group?

14. Should patients who are intolerant to erlotinib/gefitinib be able to switch to osimertinib? If so, should intolerance be further defined? Should a timeframe for switching be specified?

15. If osimertinib was to be funded as a first-line treatment, what impact would this have on erlotinib and gefitinib use? Would there be a desire clinically to use these agents in a later line setting?

16. Would the use of osimertinib create any significant changes in health-sector expenditure other than for direct treatment costs (e.g. diagnostic testing, nursing costs or treatment of side-effects)?

Recommendations

17. Should osimertinib be listed as a first-line treatment for locally advanced or metastatic EGFRm positive NSCLC in the Pharmaceutical Schedule?

    - Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.

18. Are the proposed Special Authority criteria appropriate?

    18.1. If osimertinib were to be funded in a first-line setting, should amendments be made to the criteria for erlotinib/gefitinib? If so, in what way? Please also describe the evidence to support the recommended criteria changes (if applicable).

19. If listing is recommended, what priority rating would you give to this proposal? Low / medium / high / only if cost-neutral?

20. Does the Committee have any recommendations additional to the application?

Second-line indication:

21. Does the Committee consider that the AURA3 results submitted are sufficient to address previous concerns regarding the lack of longer follow-up data and make a further recommendation for osimertinib for the treatment of EGFR T790M mutation-positive NSCLC second-line after prior EGFR TKI therapy?

    21.1. If yes, should osimertinib be funded for the treatment of EGFR T790M mutation-positive NSCLC second-line after prior EGFR TKI therapy?

    21.2. If listing is recommended, what priority rating would you give to this proposal? Low / medium / high / only if cost-neutral?

22. Does the Committee have any recommendations additional to the application?

PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Committee regarding an application from AstraZeneca for the use of osimertinib (Tagrisso) for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC.

Additionally, this paper seeks further advice on an application from AstraZeneca for the use of osimertinib (Tagrisso) for the treatment of EGFR T790M mutation-positive NSCLC second-line after prior EGFR tyrosine kinase inhibitor (TKI) therapy following the submission of additional evidence.

DISCUSSION

BACKGROUND

Previous consideration of treatments for locally advanced or metastatic EGFRm positive NSCLC:

Gefitinib and erlotinib have been previously considered as first and second-line treatments for EGFRm positive NSCLC.

Erlotinib and gefitnib are currently funded for the first line treatment of locally advanced or metastatic, unresectable, non-squamous EGFRm positive NSCLC (see further details in Need section below).

Previous consideration of osimertinib

In November 2017, PHARMAC received an application from AstraZeneca for osimertinib for the treatment of EGFR T790M mutation-positive NSCLC second-line after prior EGFR protein-TKI therapy. In April 2018, CaTSoP deferred making a recommendation pending publication of longer follow-up including mature survival data from the AURA3 trial (full submission, clinical advice paper and record available in Appendix One).

In June 2020, the supplier provided PHARMAC staff with an abstract and presentation of the final overall survival AURA3 results, as well as a clinical study overview (available in Appendix Three). The supplier has indicated that the full publication of results is expected later in 2020.

PHARMAC seeks advice from the Committee as to whether these results of the AURA3 trial provided are sufficient to overcome previous concerns regarding long term data for this agent.

Need

Description of the disease

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 (~89% in New Zealand). NSCLC can be sub-classified as squamous (~25%) or non-squamous (~75%; including adenocarcinoma and large cell histologies) histological types. The majority (~75%) of patients 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 recur following treatment and progress to advanced/metastatic disease.

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 TKI inhibitors in lung cancer.

Epidemiology

Lung cancer is the biggest cause of cancer death in New Zealand, with over 1600 deaths per year (Ministry of Health, 2016). In 2017, 2,226 lung cancer registrations were recorded in New Zealand, with an age standardised rate of 27.7 per 100,000.

Māori are disproportionately impacted by lung cancer, compared with non-Māori: In 2017, the incidence of lung cancer for Māori was 81.5 per 100,000. Lung cancer also develops earlier in Māori compared with non-Māori, incidence rates peaking at age 70-74 years for Māori (730.3 per 100,000) and age 80-84 years for non-Māori (256.9 per 100,000) (Ministry of Health, 2019).

In New Zealand, approximately 22% of NSCLC patients tested for the EGFR mutation have EGFRm positive tumours (Tin Tin et al. Cancer Epidemiol. 2018;57:24-32). Tin Tin et al. reported that Māori and patients aged over 80 years are less likely to be tested for the EGFR mutation. The EGFR mutation is observed more commonly in never-smokers, women, and patients with adenocarcinoma (Zhang et al. Oncotarget. 2016;7:78985-93). There is a higher tested and reported incidence of EGFR mutation in south-east Asian patients (40%) and Pacific patients (24%) than in New Zealand European (18%) or Māori patients (10%) (McKeage et al. 2015. Technical report for the Heath Innovation Partnership of the Health Research Council of New Zealand and National Health Committee).

Patients treated with EGFR TKIs generally develop resistance, the most common of which is T790M mutation.

The health need of the person

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, and 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, health related quality of life substantially deteriorates (Wood et al. Qual Life Res. 2019;28:1849-1861).

The availability and suitability of existing medicines, medical devices and treatments

Two first-generation tyrosine kinase inhibitors (TKIs), erlotinib (Tarceva) and gefitinib (Iressa) are currently funded for the first line treatment of locally advanced or metastatic, unresectable, non-squamous EGFRm positive NSCLC. Both are oral tablet formulations taken once daily. Following progression on erlotinib or gefitinib, patients may receive platinum-based doublet chemotherapy and then further treatment with agents such as docetaxel, paclitaxel or vinorelbine.

Erlotinib and gefitinib are currently listed on the Pharmaceutical Schedule under the following Special Authority criteria:

Erlotinib – Special Authority for Subsidy

Initial application only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:

All of the following:

1 Patient has locally advanced or metastatic, unresectable, non-squamous Non Small Cell Lung Cancer (NSCLC); and

2 There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and

3 Either:

3.1 Patient is treatment naïve; or

3.2 Both

3.2.1 The patient has discontinued gefitinib due to intolerance; and

3.2.2 The cancer did not progress while on gefitinib; and

4 Erlotinib is to be given for a maximum of 3 months

Renewal only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

Gefitinib – Special Authority for Subsidy

Initial application only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:

All of the following:

1 Patient has locally advanced, or metastatic, unresectable, non-squamous Non Small Cell Lung Cancer (NSCLC); and

2 Either:

2.1 Patient is treatment naïve; or

2.2 Both:

2.2.1 The patient has discontinued erlotinib due to intolerance; and

2.2.2 The cancer did not progress whilst on erlotinib; and

3 There is documentation confirming that disease expresses activating mutations of EGFR tyrosine kinase; and

4 Gefitinib is to be given for a maximum of 3 months

Renewal only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

The health need of family, whānau, and wider society

There is a substantial impact on the family and whānau of patients with lung cancer, particularly on those acting as caregivers. Family and whānau face physical, emotional and financial challenges that have the potential to significantly impact on their health-rated quality of life and psychological health. Caregivers of people with advanced NSCLC have impaired activity and higher rates of depression, which worsens as their loved one's condition deteriorates (Wood et al. Qual Life Res. 2019;28:1849-1861).

The impact on the Māori health areas of focus and Māori health outcomes

Māori experience a substantially higher rate of lung cancer compared with non-Māori, however experience a lower reported incidence of EGFR mutation compared with non-Māori. Māori develop lung cancer earlier in life, however, are often diagnosed at more advanced stages than non-Māori, which negatively impacts prognosis. Lung cancer accounts for nearly one third of all Māori cancer deaths (Health Quality and Safety Commission NZ; 2016).

Lung cancer is one of the five Hauora Arotahi – PHARMAC Māori Health Areas of Focus.

The impact on the health outcomes of population groups experiencing health disparities

Lung cancer disproportionately affects people in lower socioeconomic groups. In 2017, lung cancer registrations were the greatest in deprivation quintile five, with over double the number of registrations compared to those in quintile one (Ministry of Health, 2019).

A 2012 study outlining cancer incidence rates in the New Zealand, reported pooled data from 1981 to 2004 that indicated Pacific people in New Zealand have a higher rate of lung cancer than European/other people (standardised rate ratio 1.4 (95% CI, 1.21 to 1.57) for males and 1.1 (95% CI, 0.91 to 1.31) for females) (Meredith et al. 2012).

The impact on Government health priorities

This application aligns with the Government health priority of cancer. Specifically, lung cancer is a focus for PHARMAC under the Hauora Arotahi Māori health areas of focus.

Health Benefit

Details of the pharmaceutical under consideration

Clinical Pharmacology and Mechanism of Action

Osimertinib is an orally administered third generation TKI. It is a selective and irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harbouring single (L858R or del746-750) or double (L858R/T790M or del746 750/T790M) mutations.

New Zealand Regulatory Approval

Tagrisso is registered with the indication for the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumours have EGFR mutations; and for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC.

Recommended Dosage

80 mg taken orally once a day at the same time, without regard to food. If dose reduction is required (based on individual safety and tolerability), 40 mg once a day.

Proposed Treatment Paradigm

Osimertinib is proposed to be used in the first-line treatment of patients with locally advanced or metastatic EGFRm NSCLC as a monotherapy. The supplier has indicated that osimertinib would sit alongside erlotinib and gefitinib in the first line setting. We seek the Committee's advice regarding the impact funding osimertinib may have on the use of current EGFR TKIs.

The green box highlighted in figure two indicates the application AstraZeneca sought funding for in 2017 (second-line, EGFRm T790M positive NSCLC), which received a defer recommendation from CaTSoP in 2018.

Fig 1. Current treatment paradigm

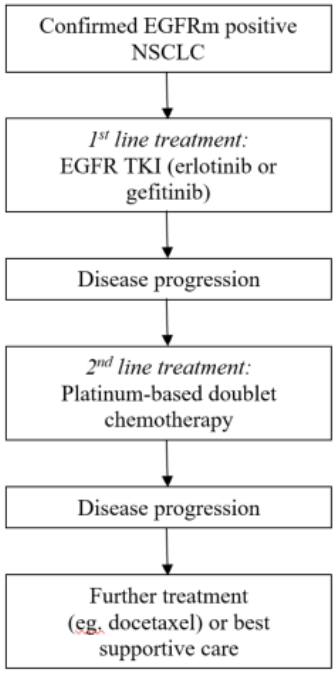
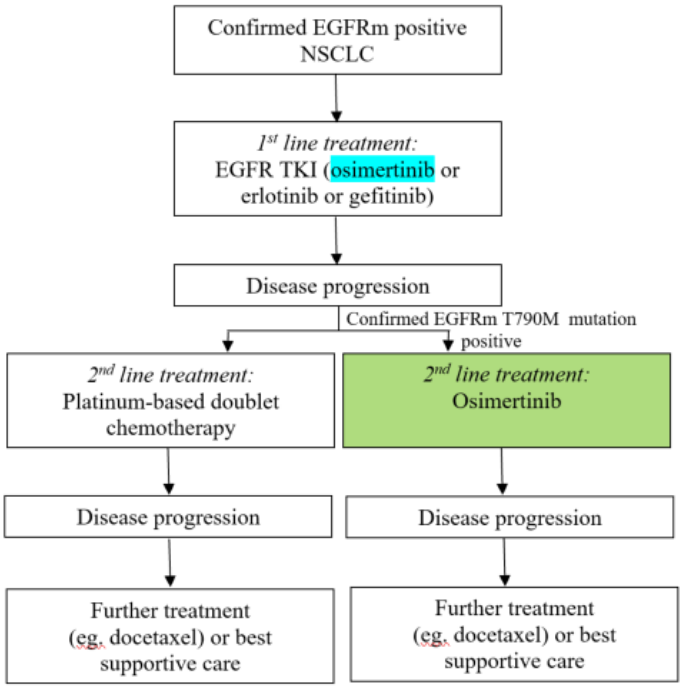


Fig 2. Proposed treatment paradigm



EGFR, epidermal growth factor; TKI, tyrosine kinase inhibitor.

Proposed Special Authority Criteria

The following Special Authority criteria was submitted by the applicant (mainly structural amendments have been made by PHARMAC staff to align with currently funded TKI special authority criteria).

Osimertinib – Special Authority for Subsidy

Initial application only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:

All of the following:

1 Patient has locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous Non-Small Cell Lung Cancer (NSCLC); and

2 Either

2.1 Patient is treatment naïve; or

2.2 Both

2.2.1 The patient has discontinued gefitinib or erlotinib due to intolerance; and

2.2.2 The cancer did not progress while on gefitinib or erlotinib; and

3 There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and

4 Treatment must be used as monotherapy; and

5 Patient must have a WHO performance status of 2 or less

Renewal only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

International Recommendations

Table 1: International recommendations regarding the funding of osimertinib for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC

Country (HTA Agency)	Meeting Date	Outcome	Reason
Australia (PBAC)	July 2019	✗ The PBAC did not recommend osimertinib for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC.	The PBAC noted that the magnitude of benefit in overall survival was uncertain, as the data provided were still immature. The PBAC considered the incremental cost effectiveness ratio per quality adjusted life years was unacceptably high and uncertain at the proposed price. The PBAC also considered that the estimated PBS population for first-line use was likely to be overestimated and the length of treatment was uncertain.
Canada (CADTH - CDEC)	January 2019	✓ The pERC recommended reimbursement of osimertinib in the first-line treatment of patients with locally advanced (not	The pERC was confident of the net clinical benefit of osimertinib (based on improved progression-free survival).

Country (HTA Agency)	Meeting Date	Outcome	Reason
		amendable to curative intent therapy) or metastatic NSCLC whose tumours have EGFR mutations (exon 19 deletions or exon 21 (L858R)), provided that the cost-effectiveness is improved and that the budget impact is addressed. If the above conditions cannot be met, the pERC does not recommend reimbursement of osimertinib. To date, it does not appear that it has been reimbursed.	The pERC also considered that osimertinib had a manageable side effect profile which did not decrement a patient's quality of life. The pERC concluded that the price submitted was not cost-effective compared to standard TKIs.
Scotland (SMC)	August 2019	✗ The SMC did not recommend osimertinib as monotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR mutations.	The SMC consider that the submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.
UK (NICE)	January 2020	✗ The NICE did not recommend osimertinib for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults.	No direct evidence comparing osimertinib with afatinib, which may be more effective than erlotinib and gefitinib. The most plausible cost-effectiveness estimates are above what NICE normally considers an acceptable use of NHS resources. Osimertinib does not meet NICE's criteria to be included in the Cancer Drugs Fund because it does not have the potential to be cost effective at the price offered.

The health benefits to the person, family, whānau and wider society

Evidence Summary

The supplier has identified seven trials that provide the primary evidence for the health benefits of osimertinib for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC. A summary of these trials is provided in the table below (Table 2).

Table 2: Summary of evidence for osimertinib for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC

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-occurring with other EGFR mutations. Median age, 64 years.	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
FLAURA	FLAURA trial, as described above.	FLAURA trial population, as described above.	FLAURA trial population, as described above. 200 patients with available	FLAURA trial intervention, as described above.	Median follow-up for CNS PFS: 12.4 months for osimertini	• CNS progression was reported in 20% (n=12 of 61) of patients in the osimertinib group versus 39% (n=26 of 67) of patients in the comparator group.	Similar AEs as reported in wider FLAURA study.	Reungwetwattana et al. J Clin Oncol. 2018;36:3290-3297.

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
		Brain scans were only mandated in patients with known or suspected CNS metastases at baseline.	brain scans (128 had measurable and/or unmeasurable CNS lesions).		b and 7.0 months for the comparator.	• The estimated probability of observing a CNS progression event (in the absence of a non-CNS progression event or death) at 6 months was 5% (95% CI=1-13) with osimertinib vs 18% (95% CI=10-28) in the comparator group. At 12 months: 8% (95% CI=3-16) with osimertinib vs 24% (95% CI=15-35) with the comparator.		
FLAURA	FLAURA trial, as described above.	As above. Asian patients enrolled at Asian sites in FLAURA trial. >90% metastatic disease.	n=322 Osimertinib n=162; Comparator n=160 (gefitinib, n=130; erlotinib, n=30).	FLAURA trial intervention, as described above.	Median follow-up for PFS: 13.8 months for osimertinib and 10.7 months for comparator.	Median duration of treatment: 15.5 months for osimertinib, 11.7 months for comparator. • Median PFS 16.5 months (95% CI: 13.8–20.7) in the osimertinib group and 11.0 months (95% CI: 9.5–12.6) in the comparator group. HR for disease progression or death =0.54, 95% CI=0.41–0.72, p<0.0001. • Survival rates at 18 months were 82% (95%: CI: 75–88) with osimertinib and 72% (95% CI: 64–79) with comparator. HR for death = 0.65, 95% CI: 0.42 1.02, p=0.0609. • OS data immature at interim analysis.	• 99% of all patients experienced an AE. • Fewer grade 3 or higher AEs occurred with osimertinib than comparator (40% vs 48%). • Three most common AEs in osimertinib and comparator were rash (58% and 81%, respectively), diarrhoea (54% in each group), and paronychia (40% and 37%).	Cho et al. J Thorac Oncol. 2019;14:99-106

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
FLAURA	FLAURA trial, as described above.	FLAURA trial population, as described above.	FLAURA trial population, as described above.	FLAURA trial intervention, as described above.	Median time to discontinuation: 20.8 months in the osimertinib group and 11.5 months in the comparator.	*Randomised treatment:* Treatment beyond disease progression was allowed if the investigator judged continued clinical benefit (median duration of treatment beyond progression was 8.1 weeks for osimertinib and 7.0 weeks for comparator). *Subsequent treatment:* • At data cut off, 138 of 279 (49%) and 213 of 277 (77%) patients discontinued osimertinib and comparator, respectively; 82 (59%) of the osimertinib and 129 (61%), of the comparator groups, started a subsequent treatment. • At data cut off, 73 patients (26%) in the osimertinib and 106 (38%) of the comparator, group had second progression events or died. • Median 2PFS**:** not reached (95% CI=23.7–NC) in the osimertinib group and 20.0 months (95% CI=18.2–NC) in the comparator group. HR, 0.58; 95% CI=0.44–0.78; p=0.0004. (2PFS: time from randomization to first subsequent progression or death).	Not reported.	Planchard et al. Clin Cancer Res.2019;25: 2058-2064.

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
FLAURA.	FLAURA trial, as described above.	FLAURA trial population, as described above. Mean age: 67 years <90% metastatic disease in each group.	n=120 Osimertinib n=65; gefitinib n=55	Osimertinib (80 mg daily) or gefitinib (250 mg once daily).	Median follow up period not reported.	Median treatment exposure: 15.3 months for osimertinib group and 11.0 months for gefitinib. • Median PFS: 19.1 months (95% CI=12.6-23.5) osimertinib and 13.8 months (95% CI=8.3-16.6) gefitinib. HR=0.61; 95% CI=0.38-0.99 [subgroup analysis not powered for p value calculation]. • Disease progression occurred in 34 (52.3%) patients in the osimertinib group and 36 (65.5%) in the gefitinib group. • Median OS not reached (immature data).	• AEs Grade 3 or higher were reported in 31 (47.7%) patients in the osimertinib group and 31 (56.4%) patients in the gefitinib group. • Only one AE leading to death was reported (in the gefitinib group). • AEs leading to discontinuation were reported in 17 (26.2%) patients in the osimertinib group and 19 (34.5%) patients in the gefitinib group.	Ohe et al. Jpn J Clin Oncol. 2019;49:29-36.
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 overall survival 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	• 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	Ramalingam et al. N Engl J Med. 2020;382:41-50

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
						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).	treatment discontinuation due to AEs were similar in the two groups, despite the longer duration of exposure to osimertinib.	
FLAURA	FLAURA trial, as described above. Patients completed the EORTC QLQ-LC13 weekly for 6 weeks, then every 3 weeks, and the QLQ-C30	FLAURA trial population, as described above.	FLAURA trial population, as described above.	FLAURA trial intervention, as described above.	The median duration of PFS follow-up: 15.0 months for osimertinib and 9.7 months for comparator. Scores were assessed from	Median duration of treatment was 16.2 months for osimertinib arm and 11.5 months for comparator. A ≥10 point change threshold for clinical relevance was predefined. • None of the improvements in key symptoms reached the threshold for clinical relevance • QoL improvements in the osimertinib group were greater than in the comparator group for emotional functioning (8.79 vs 4.9; p=0.004) and social functioning (7.66 vs 1.74; p<0.001).	• None reported.	Leighl et al. Eur J Cancer. 2020;125:49-57.

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety	Citation
	every 6 weeks.				randomisation until study treatment discontinuation.	• Cognitive functioning remained stable in the osimertinib group but deteriorated in the comparator group (0.03 vs 3.91; p=0.005).		

PFS, progression-free survival; AE, adverse event; OS, overall survival; CI, confidence interval.; HR, hazard ratio; NC, not calculable; ORR, objective response rate.

PHARMAC staff note that there are numerous ongoing trials investigating the use of osimertinib in combination with other treatments, including in combination with chemotherapy.

Literature Search

PHARMAC staff conducted a PubMed search (search terms: osimertinib AND NSCLC AND first line) and did not identify any additional publications regarding osimertinib for first line NSCLC that were not identified by the supplier.

Consequences for the health system

None identified.

Suitability

The features of the medicine or medical device that impact on use

Osimertinib is a tablet taken once daily, as with the other drugs in this class – erlotinib and gefitinib. Unlike erlotinib, osimertinib can be taken without regard to food.

Leighl et al. demonstrated that patients who received osimertinib demonstrated statistically significantly greater emotional and social functioning compared to patients who were treated with erlotinib or gefitinib; additionally patients treated with osimertinib were observed to maintain stable social functioning (unlike the deterioration observed in erlotinib or gefitinib patients) (Leighl et al. Eur J Cancer. 2020;125:49-57).

Costs and Savings

PICO (Population, Intervention, Comparator, Outcome)

Table 3 below summarises PHARMAC staff's interpretation of the PICO for osimertinib if it were to be funded in New Zealand for locally advanced or metastatic EGFRm NSCLC.

This PICO captures key clinical contexts, helping review the proposal and frame any future economic assessment by PHARMAC. We seek CaTSoPs advice on the content in the table below.

Note that the PICO may change as clinical and other features evolve.

Table 3**:** PICO for osimertinib if it were to be funded in New Zealand for locally advanced or metastatic EGFRm NSCLC

Population	Patients with locally advanced (Stage lllb) or metastatic (Stage lV), non-squamous Non-Small Cell Lung Cancer (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 have not progressed disease
Intervention	One osimertinib 80 mg tablet per day until disease progression or unacceptable toxicity.
Comparator(s) (NZ context)	For treatment naïve patients: erlotinib, one 150 mg tablet daily or gefitinib, one 250 mg tablet daily, until disease progression or unacceptable toxicity For patients who are intolerant to gefitinib: the comparator is erlotinib, one 150 mg tablet daily. For patients who are intolerant to erlotinib: the comparator is gefitinib, one 250 mg tablet daily. For patients who are intolerant to both gefitinib and erlotinib, the comparator is placebo.
Outcome(s)	Extending progression free survival (PFS) and overall survival (OS). The FLAURA trial reported the median PFS in first-line treatment of EGFR mutation–positive advanced NSCLC with osimertinib was 18.9 months vs 10.2 months with erlotinib or gefitinib. It also reported the median overall survival was 38.6 months in the osimertinib group and 31.8 months in the erlotinib/gefitinib group.
Table definitions: **P**opulation: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup) **I**ntervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation). **C**omparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation). **O**utcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.	

Costs and savings to pharmaceutical expenditure

Cost per patient

The applicant recommends the daily dose to be 80 mg (one 80 mg tablet). The price, including a confidential proposed rebate, is S 9(2)(b) (ii) 9(2) for 1 pack containing 30 tablets of 80 mg (30 days' worth at recommended dose). This results in a price per person per year of S 9(2)(b) (ii) 9(2).

This compares to the confidential price S 9(2)(b) (ii) 9(2) per person per year for gefitinib (net S 9(2) (b)(ii) per pack of 31 pills) and S 9(2)(b) (ii) 9(2) for erlotinib (net S 9(2)(b) (ii) 9(2) per 30 days of pills).

The duration of treatment is until disease progression, at which point the patient begins platinum-based doublet chemotherapy. The FLAURA trial reported a median PFS of 18.9 months, resulting in a treatment cost of S 9(2)(b)(ii), 9(2)(ba)(i) & per patient.

Osimertinib is a community pharmaceutical, so patients who would otherwise not be on treatment (those who are intolerant to both erlotinib and gefitinib) would have an increase in pharmacy prescription co-payments.

Estimated Incremental Total Cost of Listing

The supplier estimates that:

- S 9 (2)(b) prevalent patients would be eligible for treatment in the first year of funding, with approximately S 9 (2) incident patients each year thereafter, with S 9 (2)(b) patients in the final year (year 5).
- An initial uptake of osimertinib to be 65%, increasing to 90% in year 5.

PHARMAC staff consider the numbers of patients provided by the supplier do not align with PHARMhouse dispensing data, and that several of the supplier's assumptions around the eligible population seem unreasonable. Using dispensing data for erlotinib and gefitinib, and assuming a small amount of growth in the patient pool based on a growing 65+ aged population, PHARMAC staff estimate the current incidence of patients with EGFRm NSCLC using TKIs is approximately 150 patients per year (65% erlotinib, 35% gefitinib). As the median PFS time for erlotinib and gefitinib is 10 months, PHARMAC staff calculations did not carry these patients over to the next year and only considered their cost of treatment for 10 months of the year in which treatment was started. For osimertinib, PHARMAC staff included a six month cost of treatment in the year after beginning treatment, as median PFS is closer to 18 months.

Based on these revised patient numbers and the treatment duration from the trial, the estimated budget impact of funding osimertinib for EGFRm NSCLC patients (as described in the PICO above) in year 1 changes to S 9(2)(b)(ii), 9 (2)(ba)(i) & 9, increasing to S 9(2)(b)(ii), 9 (2)(ba)(i) & 9 in year 5, with a 5-year NPV of S 9(2)(b)(ii), 9 (2)(ba)(i) & 9 discounted at 8%.

	Year 1	Year 2	Year 3	Year 4	Year 5	NPV
New patients each year	S 9 (2)	S 9 (2)	S 9 (2)	S 9 (2)	S 9 (2)	
Cost of intervention (million)	S 9(2) (b)(ii)	S 9(2) (b)(ii)	S 9(2) (b)(ii)	S 9(2) (b)(ii)	S 9(2) (b)(ii)	
Cost of status quo (million)	S 9 (2)(b)	S 9 (2)(b)	S 9 (2)(b)	S 9 (2)(b)	S 9 (2)(b)	
Incremental cost (million)	S 9(2)(b) (ii), 9(2)	S 9(2)(b) (ii), 9(2)	S 9(2)(b) (ii), 9(2)	S 9(2)(b) (ii), 9(2)	S 9(2)(b) (ii), 9(2)	S 9(2)(b) (ii), 9(2)
Note: BIA does not consider any future price drops that could occur as a result of generic entry or ongoing competitive processes in either the intervention or status quo over the consider 60 month time period.						

Costs and savings to the rest of the health system

Funding osimertinib through the community would incur a 4% dispensing mark-up per pack which, on a list price of $9,310, is S 9(2)(b)(ii) per pack or S 9(2)(b)(ii) 9(2) per patient per year.

This is in comparison to S 9(2)(b)(ii) per patient per year for gefitinib, and S 9(2)(b)(ii) for erlotinib.

Cost Effectiveness (combining the Health Benefits and Costs quadrants)

The supplier has not provided an economic analysis of osimertinib for EGFRm NSCLC patients with their submission. PHARMAC staff may assess the cost-effectiveness of osimertinib in this setting following a positive clinical advice recommendation.

APPENDICES

Appendix 1: Previous consideration of osimertinib

- Submission for osimertinib for locally advanced or metastatic EGFR T790M NSCLC
- 2018-04 CaTSoP Record
- 2018-04 CaTSoP paper

Appendix 2: Evidence

- Cho et al. J Thorac Oncol. 2019;14:99-106
- Leighl et al. Eur J Cancer. 2020;125:49-57.
- Ohe et al. Jpn J Clin Oncol. 2019;49:29-36.
- Planchard et al. Clin Cancer Res.2019;25:2058-2064.
- Ramalingam et al. N Engl J Med. 2020;382:41-50
- Reungwetwattana et al. J Clin Oncol. 2018;36:3290-3297.
- Soria et al. N Engl J Med. 2018;372:113-125

Appendix 3: Additional information (EGFR T790M indication)

- AURA III study abstract
- ESMO-ASIA presentation of the final OS analysis of AURA3 trial, 22 November 2019
- Clinical study overview from AURA3, which contains more detail of these findings.

THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system

PHARMAC
TE PĀTAKA WHAIORANGA

PHARMACEUTICAL SCHEDULE APPLICATION

To: CaTSoP

From: Funding Application Advisor

Date: March 2021

Osimertinib for the first-line treatment of locally advanced or metastatic epidermal growth factor receptor mutation (EGFRm) non-small cell lung cancer (NSCLC); and

Osimertinib for the second-line treatment of EGFR T790M mutation-positive NSCLC after prior EGFR tyrosine kinase inhibitor (TKI) therapy

SUMMARY OF PHARMACEUTICAL			
Brand Name	Tagrisso	**Chemical Name**	Osimertinib
Indications	First-line (1L) treatment of adult patients with locally advanced or metastatic EGFRm NSCLC; and Second-line (2L) treatment of patients with locally advanced or metastatic EGFRm NSCLC with T790 mutation	**Presentation**	40 mg and 80 mg tablets
		Dosage	80 mg once a day
Therapeutic Group	Oncology and Immunosuppressants	**Application Date**	1L: December 2019 2L: November 2017
Supplier	AstraZeneca		
MOH Restrictions	Prescription medicine	**Proposal type**	New listing
Current Subsidy	NA	**Proposed Restriction**	Special Authority
Proposed Subsidy	$9,310 (gross price) per 30 tablets irrespective of strength (net price of S 9(2) per pack)*	**Manufacturer's Surcharge**	Nil
First line Market Data	**Year 1**	**Year 2**	**Year 3**
Number of Patients†	S 9	S 9	S 9
Net Cost to Schedule†	S 9(2)(b)	S 9(2)(b)	S 9(2)(b)
Net Cost to DHBs (5-year NPV, 8%)	S 9(2)(b)		
Second line Market Data	**Year 1**	**Year 2**	**Year 3**
Number of Patients†	S 9	S 9	S 9
Net Cost to Schedule†	S 9(2)(b)	S 9(2)(b)	S 9(2)(b)
Net Cost to DHBs (5-year NPV, 8%)	S 9(2)(b)		

DHBs, District health board; MOH, Ministry of Health; NPV, Net Present Value.
*Confidential price offer in 2019 application for funding in a first line setting. Note: price could differ between the lines of therapy given the difference in population numbers. See budget impact in cost and saving section below for more information.
†Supplier estimate.

QUESTIONS TO CATSOP

First-line treatment of locally advanced or metastatic EGFRm positive NSCLC

1. Noting previous PTAC records for this proposal, does the Subcommittee have any additional comments regarding the health need of this patient group, including any unmet health need?
2. Do the treatment paradigms outlined by PHARMAC staff in figure 1 on page 9 accurately reflect the current and proposed treatment paradigms across New Zealand? If no, what should be adjusted?
3. Does the information in the PICO table (Table 1) accurately reflect the intended population, intervention, comparator and outcome, if osimertinib were funded for the first line treatment of locally advanced or metastatic EGFRm positive NSCLC? If not, how should this be adjusted?

    3.1. What proportions of first-line TKI usage does the Subcommittee consider would change to osimertinib, once it is an established treatment in the paradigm as a first-line treatment?

        3.1.1 Of the remaining patients would the Subcommittee expect the relative proportion of patients receiving first-line gefitinib and erlotinib to remain unchanged? (i.e. a greater number of patients taking erlotinib than gefitinib).

    3.2. Would the total number of patients receiving first-line TKI treatment increase if osimertinib was funded for first-line use? If yes, by how much?

    3.3. What would the Subcommittee consider a reasonable uptake assumption for osimertinib, if it were funded in this setting?

4. Should patients be able to switch to osimertinib from currently funded TKI's for reasons other than intolerance? If yes, how many patients could be expected to do this?
5. Would the funding of osimertinib have any impact on the wider NSCLC treatment paradigm? If so, how?

    5.1. Should patients who have received osimertinib first-line be able to access gefitinib/erlotinib as a second line treatment prior to platinum-based chemotherapy?

6. What is the Subcommittee's view of the patient number estimates by PHARMAC staff?
7. Does the osimertinib tablet formulation offer any suitability benefits compared to current funded first-line treatments (ie non-clinical features that may impact on use, either by the patient, by family/whānau, or by healthcare workers, that have not been considered in the application)?

Recommendation

8. Are the proposed Special Authority criteria for osimertinib in the first-line setting appropriate? If not, how should these be adjusted?

9. Should osimertinib be listed in the Pharmaceutical Schedule for **first-line treatment of EGFRm positive NSCLC**?

    - Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.

10. If listing is recommended, what priority rating would you give to this proposal (within the context of treatment of malignancy)? **[low / medium / high / only if cost-neutral]**?

11. Does the Subcommittee have any other comments or recommendations about this first-line application?

Second-line treatment of EGFR T790M mutation-positive NSCLC after prior EGFR tyrosine kinase inhibitor (TKI) therapy

1. Noting previous CaTSoP and PTAC records for this proposal, does the Subcommittee have any additional comments regarding the health need of this patient group, including any unmet health need?

Based on the updated evidence provided with this paper:

2. Does osimertinib second-line treatment provide any additional health benefit (including a quality of life benefit) or create any additional risks compared with other funded treatment options? If so, what benefits or risks are different from alternative treatments?

    2.1. Is any other evidence required to inform assessment of risks/benefits (including the magnitude of benefit) of osimertinib in this setting? If so, what is required?

3. Which patient population would benefit most from osimertinib in the second-line (eg patients with CNS metastases)?

4. What is the strength and quality of evidence, including its relevance to NZ, for health benefits that may be gained from osimertinib second-line treatment?

    4.1. Is the evidence applicable to New Zealand patients in terms of mutation profile?

5. Would osimertinib second-line produce a health benefit for family, whānau or wider society, additional to the health benefits for people with EGFR T790M positive NSCLC? If so how, and what is the strength and quality of evidence for this benefit?

6. If osimertinib were to be funded for second-line treatment of EGFR T790M positive NSCLC, would there be any additional requirements or consequences for the health system (eg re-biopsy, T790M testing, or plasma circulating tumour DNA testing)?

    6.1. Are tests for T790M and/or plasma circulating tumour DNA performed for standard of care of patients with NSCLC across New Zealand?

        - If so, which tests and when are they used (eg at diagnosis, post disease progression on a TKI)?

    6.2. If used in NZ, are T790M tests able to accurately confirm T790M mutation status?

7. If osimertinib were funded for first-line and second-line use, would it be appropriate for patients with T790M positive NSCLC to receive funded treatment with osimertinib twice?

    7.1. If not, would patients likely receive osimertinib in the first line or second line?

7.2. Do the treatment paradigms outlined by PHARMAC staff in figure 1 on page 9 accurately reflect the current and proposed treatment paradigms? If no, what changes need to be made?

8. Does the information in the PICO table (Table 5) accurately reflect the intended population, intervention, comparator and outcome, if osimertinib were to be funded for second-line treatment of locally advanced or metastatic EGFRm T790M positive NSCLC? If not, how should this be adjusted?

9. What is the Subcommittee's view of the patient number estimates by PHARMAC staff?

   9.1. Would the Subcommittee expect there to be an eligible pool of prevalent patients at the time of funding? If yes, how many eligible prevalent patients would you expect?

   9.2. What would the Subcommittee consider a reasonable uptake assumption for osimertinib, if funded in this setting?

10. Would the use of osimertinib create any significant changes in health-sector expenditure other than for direct treatment costs (e.g. disease monitoring costs, adverse event management, use of subsequent lines of therapy).

11. Does the osimertinib tablet formulation offer any suitability benefits compared to current funded second-line treatments (ie non-clinical features that may impact on use, either by the patient, by family/whānau, or by healthcare workers, that have not been considered in the application)?

Recommendation

12. Are the proposed Special Authority criteria for osimertinib in the second-line setting appropriate? If not, how should these be adjusted?

13. Should osimertinib be listed in the Pharmaceutical Schedule for **second-line treatment of EGFR T790M positive NSCLC**?

    - Name the Factors for Consideration particularly relevant to a positive or negative recommendation and explain why each is relevant.

14. If listing is recommended, what priority rating would you give to this proposal (within the context of treatment of malignancy)? **[low / medium / high / only if cost-neutral]**?

15. Does the Subcommittee have any other comments or recommendations about this application?

PURPOSE OF THIS PAPER

The purpose of this paper is to seek advice from the Subcommittee regarding:

1. Osimertinib for the first-line treatment of locally advanced or metastatic Epidermal Growth Factor Receptor mutation (EGFRm) positive non-small cell lung cancer (NSCLC), following review of this application by PTAC; and
2. Osimertinib for the second-line treatment of EGFR T790M mutation-positive NSCLC after prior EGFR tyrosine kinase inhibitor (TKI) therapy, in light of updated evidence from the AURA3 trial's final overall survival analysis.

This paper discusses the treatment paradigm for EGFRm NSCLC and each of these osimertinib proposals in turn. In addition, some brief general background information about EGFRm NSCLC and osimertinib is provided below.

BACKGROUND

Previous consideration of treatments for locally advanced or metastatic EGFRm positive NSCLC

Currently funded treatments

Two first-generation tyrosine kinase inhibitors (TKIs), erlotinib (Tarceva) and gefitinib (Iressa) are currently funded for the first line treatment of locally advanced or metastatic, unresectable, non-squamous EGFRm positive NSCLC. Both are oral tablet formulations taken once daily. Following progression on erlotinib or gefitinib, patients may receive platinum based doublet chemotherapy and then after subsequent progression, receive treatment with docetaxel.

Erlotinib and gefitinib are currently listed on the Pharmaceutical Schedule under the following, essentially identical, Special Authority criteria:

> **ERLOTINIB – Special Authority for Subsidy**
> Initial application only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1 Patient has locally advanced or metastatic, unresectable, non-squamous Non Small Cell Lung Cancer (NSCLC); and
> 2 There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and
> 3 Either:
> 3.1 Patient is treatment naïve; or
> 3.2 Both
> 3.2.1 The patient has discontinued gefitinib due to intolerance; and
> 3.2.2 The cancer did not progress while on gefitinib; and
> 4 Erlotinib is to be given for a maximum of 3 months
>
> **Renewal** only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.
>
> **GEFITINIB – Special Authority for Subsidy**
> Initial application only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
> All of the following:
> 1 Patient has locally advanced, or metastatic, unresectable, non-squamous Non Small Cell Lung Cancer (NSCLC); and
> 2 Either:

2.1 Patient is treatment naïve; or
2.2 Both:
2.2.1 The patient has discontinued erlotinib due to intolerance; and
2.2.2 The cancer did not progress whilst on erlotinib; and
3 There is documentation confirming that disease expresses activating mutations of EGFR tyrosine kinase; and
4 Gefitinib is to be given for a maximum of 3 months

Renewal only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

Previous consideration of osimertinib

Osimertinib has been previously considered by PHARMAC for the following indications:

- First-line treatment of locally advanced or metastatic EGFRm positive NSCLC
    - Application received December 2019
    - Considered by PTAC in August 2020, who recommended it be funded for this indication if cost-neutral to current first-line TKI's.
- Second-line treatment of EGFR T790M mutation-positive NSCLC after prior EGFR tyrosine kinase inhibitor (TKI) therapy
    - Application received November 2017
    - Considered by CaTSoP in April 2018, who recommended it be deferred pending publication of longer-term follow-up data including mature AURA-3 survival data
    - Correspondence from AstraZeneca and from an Auckland Oncologist regarding osimertinib considered by CaTSoP in September 2018, who reiterated that publication of longer-term data (including AURA-3 trial data) was awaited
    - Updated AURA3 study materials provided by the supplier in in June 2020. Considered by PTAC in August 2020, who recommended the application be deferred pending publication and peer-review of AURA-3 overall survival results

The relevant excerpts from these clinical advice records, clinical advice papers (with appendices), the correspondence considered by CaTSoP in September 2018 and the additional materials provide in June 2020 are available in Appendix 1.

The following sections describe the treatment paradigm for patients with metastatic non-squamous EFGRm NSCLC, and the previous consideration of each osimertinib application by CaTSoP and PTAC, as applicable.

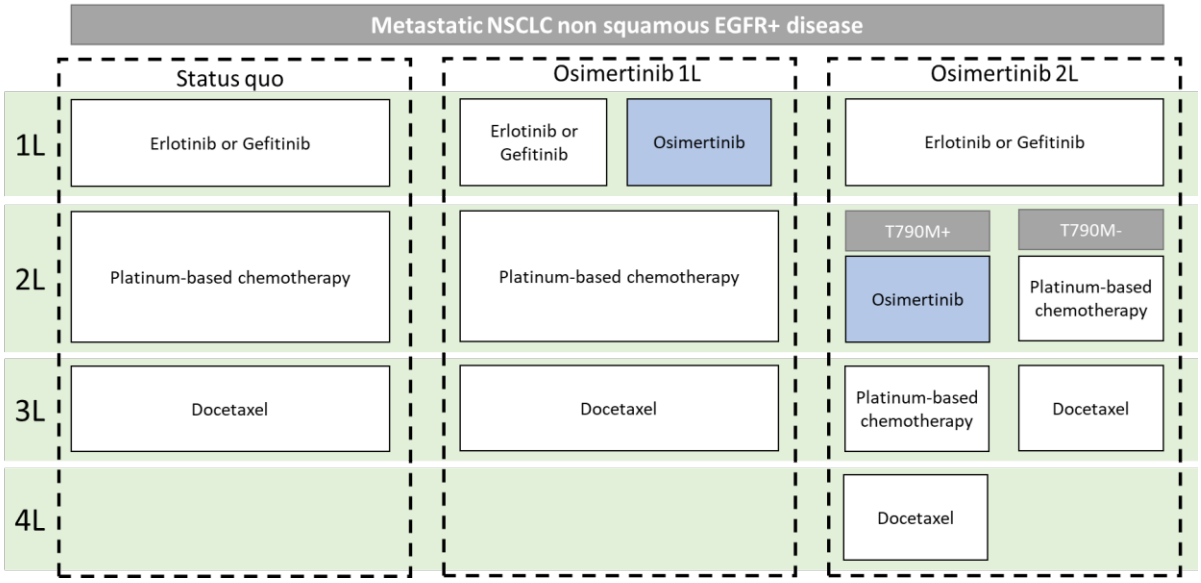
TREATMENT PARADIGM

PHARMAC's understanding of the current treatment paradigm for patients with metastatic non-squamous EFGRm NSCLC is outlined in Figure 1, below. This figure also outlines how the treatment paradigm would be expected to look if osimertinib were to be funded in either the first-line (1L) or second-line (2L) setting.

PTAC and PHARMAC staff seek the Subcommittee's advice regarding the likely sequence of treatments for EGFRm positive NSCLC, if osimertinib were funded for this indication. In particular, PHARMAC seeks the subcommittee's advice on:

- What changes, if any, need to be made to Figure 1 to accurately reflect the current treatment paradigm across New Zealand in this patient group, and what it would be expected to look like if osimertinib were funded in each setting (1L or 2L)?
- If osimertinib were funded for both 1L and 2L use:
    - Would patients with T790M+ disease receive osimertinib in both the 1L and 2L settings?
    - If only one line of osimertinib treatment was funded per-patient-lifetime, would patients with EGFRm T790M disease be more likely to have osimertinib first line treatment or second line?
- Would patients who have not yet commenced 2L treatment switch to osimertinib for reasons other than intolerance to the existing TKI treatments?
    - If yes, how many patients would you expect this would be applicable to?
- Would the funding of osimertinib affect other parts of the current NSCLC treatment paradigm? Noting the current recommendations for the funding of a PD-1 and PD-L1 agent exclude patients with EGFR and ALK mutations?

Figure 1. Current and proposed treatment paradigms for EGFR+ NSCLC in New Zealand



OSIMERTINIB FIRST LINE – EGFRM+ NSCLC

First-line treatment of locally advanced or metastatic EGFRm positive NSCLC

Background

The application for osimertinib for the first-line treatment of EGFRm NSCLC was reviewed by PTAC in August 2020. The recommendation PTAC made following its review is outlined below. The full record of the meeting is available in Appendix 1.

10.5. The Committee **recommended** that osimertinib for the first-line treatment of EGFRm NSCLC be funded if cost-neutral to current first-line pharmaceuticals in this indication, due to:

- 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; and
- High quality, randomised-control trial evidence that reported benefit in progression free survival compared with the comparator (gefitinib or erlotinib); and
- Uncertain evidence regarding benefit in overall survival compared with the comparator (erlotinib or gefitinib); and
- The lack of evidence of superiority of osimertinib to the current two first-line pharmaceuticals for this indication.

10.6. The Committee considered that PHARMAC could seek subsequent advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP) regarding the sequence of treatments in this indication, and appropriate Special Authority criteria for osimertinib in the first-line setting.

The subsequent sections of this paper focus on the specific aspects of the application that PTAC requested advice be sought from CaTSoP on, in addition to additional queries from PHARMAC staff.

Special Authority criteria

The following Special Authority criteria was submitted by the applicant for osimertinib (mainly structural amendments have been made by PHARMAC staff to align with currently funded TKI special authority criteria).

PTAC and PHARMAC seek the Subcommittee's view of the proposed Special Authority criteria for osimertinib in this setting, including any adjustments that should be made to enable appropriate access, if funded.

OSIMERTINIB – Special Authority for Subsidy
Initial application only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:
1 Patient has locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous Non-Small Cell Lung Cancer (NSCLC); and
2 Either
2.1 Patient is treatment naïve; or
2.2 Both
2.2.1 The patient has discontinued gefitinib or erlotinib due to intolerance; and
2.2.2 The cancer did not progress while on gefitinib or erlotinib; and
3 There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and
4 Treatment must be used as monotherapy; and
5 Patient must have a WHO performance status of 2 or less

Renewal only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

PICO (Population, Intervention, Comparator, Outcome)

Table 1, below, summarises PHARMAC staff's interpretation of the PICO for osimertinib if it were to be funded in New Zealand for first-line treatment of locally advanced or metastatic EGFRm NSCLC.

This PICO captures key clinical contexts, helping review the proposal and frame any future economic assessment by PHARMAC. We seek CaTSoP's advice on the content in the table below.

Note that the PICO may change as clinical and other features evolve.

Table 1**:** PICO for osimertinib if it were to be funded in New Zealand for first-line treatment of locally advanced or metastatic EGFRm NSCLC

Population	Patients with locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous Non-Small Cell Lung Cancer (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.
Comparator(s) (NZ context)	For treatment naïve patients: erlotinib, one 150 mg tablet daily or gefitinib, one 250 mg tablet daily, until disease progression or unacceptable toxicity For patients who are intolerant to gefitinib: the comparator is erlotinib, one 150 mg tablet daily. For patients who are intolerant to erlotinib: the comparator is gefitinib, one 250 mg tablet daily. For patients who are intolerant to both gefitinib and erlotinib, the comparator is standard care.
Outcome(s)	Extending progression free survival (PFS) and overall survival (OS). The FLAURA trial reported the median PFS in first-line treatment of EGFR mutation–positive advanced NSCLC with osimertinib was 18.9 months vs 10.2 months with erlotinib or gefitinib. It also reported the median overall survival was 38.6 months in the osimertinib group and 31.8 months in the erlotinib/gefitinib group.

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (eg. line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

Patient numbers and budget impact assumptions.

Using dispensing data for erlotinib and gefitinib, and assuming a small amount of growth in the patient pool based on a growing 65+ aged population, PHARMAC staff estimate the current incidence of patients with EGFRm NSCLC using TKIs is approximately 150 patients per year (65% erlotinib, 35% gefitinib).

PHARMAC staff seek the Subcommittee's advice on:

- *The estimated proportion of the EGFRm patients that would be expected to take osimertinib if it were funded as a first-line treatment with similar special authority criteria as gefitinib/erlotinib? ie what would be the expected market share of the three TKI agents once osimertinib was established in the treatment paradigm?*
- *Whether it would be reasonable to expect any growth in the total population of patients with EGFRm NSCLC receiving first line treatment, if osimertinib were funded first line?*
- *What a reasonable uptake assumption for osimertinib would be, if it were funded for first line use?*

Estimated Incremental Total Cost of Listing

The supplier estimates that:

- S 9 (2)(b) prevalent patients would be eligible for treatment in the first year of funding, with approximately S 9 (2) incident patients each year thereafter, with S 9 (2)(b) patients in the final year (year 5).
- An initial uptake of osimertinib is 65%, increasing to 90% in year 5.

PHARMAC staff consider the numbers of patients provided by the supplier do not align with PHARMhouse dispensing data, and that several of the supplier's assumptions around the eligible population seem unreasonable. As mentioned, using dispensing data for erlotinib and gefitinib, PHARMAC staff estimate the current incidence of patients with EGFRm NSCLC using TKIs is approximately 150 patients per year with 65% using erlotinib and 35% using gefitinib.

As the median PFS time for erlotinib and gefitinib is 10 months, PHARMAC staff calculations did not carry these patients over to the next year and only considered their cost of treatment for 10 months of the year in which treatment was started. For osimertinib, PHARMAC staff included a six month cost of treatment in the year after beginning treatment, as median PFS is closer to 18 months.

Based on these revised patient numbers and the treatment duration from the trial, the estimated budget impact of funding osimertinib for EGFRm NSCLC patients (as described in the PICO above) in year 1 would be S 9(2)(b)(ii), 9 (2)(ba)(i) & 9, increasing to S 9(2)(b)(ii), 9 (2)(ba)(i) & 9 in year 5, with a 5-year NPV of S 9(2)(b)(ii), 9 (2)(ba)(i) & 9 discounted at 8%.

Table 2: Estimated budget impact for osimertinib if it were funded in New Zealand for first-line treatment of locally advanced or metastatic EGFRm NSCLC.

	Year 1	Year 2	Year 3	Year 4	Year 5	NPV
New patients each year	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Cost of intervention (million)						
Cost of status quo (million)						
Incremental cost (million)						
Note: BIA does not consider any future price drops that could occur as a result of generic entry or ongoing competitive processes in either the intervention or status quo over the consider 60 month time period.						

Cost Effectiveness (combining the Health Benefits and Costs quadrants)

The supplier has not provided an economic analysis of osimertinib for the first-line treatment of EGFRm NSCLC with their submission. PHARMAC staff may assess the cost-effectiveness of osimertinib in this setting following a positive clinical advice recommendation. International assessments of cost-effectiveness have been conducted by the funding agencies described below.

Australia (PBAC)

Australia most recently reviewed an application for osimertinib as a first line treatment in EGFR positive NSCLC patients in July 2020, where it was recommended for funding. The report noted that is recommended following an acceptable incremental cost-effectiveness ratio of more than 12 and 21 QALYS per million dollars spent (NZD) being achieved, amongst other factors.

The PBAC noted it was satisfied that for some patients, treatment with osimertinib significantly improved efficacy and reduced toxicity compared to other EGFR positive TKI's currently listed in Australia. The PBAC's previous concern about the uncertainty in OS gain and how it might be affected by subsequent lines of treatment, including second line osimertinib use, was resolved based on longer term data provided in the re-submission. The key drivers of the economic model were considered to be the price of osimertinib, the time point of extrapolation for OS and the number of patients receiving second line treatment including treatment with osimertinib.

PHARMAC staff have compared the evidence previously reviewed by PTAC for this indication with the evidence noted by the PBAC in July 2020; the following two pieces of evidence have not been seen by PTAC:

- 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 (Gray et al. Clin Cancer Res. 2019;25:6644 52). The authors concluded that their results support utility of cobas tissue and plasma testing to aid selection of patients with EGFRm advanced NSCLC for first-line osimertinib treatment, and considered that a lack of EGFRm detection in plasma was associated with prolonged PFS versus patients who are plasma EGFRm positive, potentially due to patients having lower tumour burden.

- Osimertinib vs standard of care (SoC) EGFR-TKI as first-line therapy in patients (pts) with untreated EGFRm advanced NSCLC: FLAURA post-progression outcomes (Planchard et al. Ann Oncol. 2018;29(Supplement 9):ix150-169). Data cut-off was June 2017, the same as that reported in publications of the primary analysis that had been reviewed by PTAC.

Both of the above are available in Appendix 2.

England and Wales (NICE)

An updated Technology Appraisal guidance was published for this application in October 2020 (TA654). Osimertinib was recommended for patients with untreated locally advanced or metastatic EGFR+ NSCLC, providing a commercial arrangement for the company is provided. NICE noted that they considered the FLAURA trial to be broadly generalisable to the patient population in England and that the immaturity of data introduces uncertainty when considering the OS benefit. Cost-effectiveness in comparison to gefitinib and afatinib was investigated, noting the latter is noted to be more efficacious than gefitinib and is not currently funded in New Zealand.

Canada (CADTH)

CADTH's Pan-Canadian Oncology Drug Review published a review in January 2019. The review recommended that osimertinib be funded as a first line treatment for EGFR+ NSCLC patients if the cost-effectiveness was improved to an acceptable level and if the budget impact was addressed. In this recommendation, they noted a considerable improvement in PFS that was statistically significant and clinically meaningful and that it was a treatment with a manageable side-effect profile that did not result in a quality-of-life decrement. In terms of cost-effectiveness the review noted that the model was sensitive to PFS extrapolation method and whether time to progression or treatment duration was modelled. Cost-effectiveness in comparison to gefitinib and afatinib was investigated, noting the latter is noted to be more efficacious than gefitinib and is not currently funded in New Zealand.

PHARMAC
TE PĀTAKA WHAIORANGA

OSIMERTINIB SECOND LINE – EGFR T790M MUTATION+ NSCLC

Background

In November 2017, PHARMAC received an application from AstraZeneca for osimertinib for the second-line treatment of EGFR T790M mutation-positive NSCLC after prior EGFR TKI therapy.

In April 2018, CaTSoP reviewed the application and recommended it be deferred pending publication of longer-term follow-up data including mature survival data from the AURA3 trial (clinical advice paper and meeting record excerpt available in **Appendix 1**).

PHARMAC received correspondence from the supplier, AstraZeneca, in response to CaTSoP's 2018 record and a letter of support from the Auckland Lung Medical Oncology Team, which were both considered by CaTSoP at the September 2018 meeting. At that time, the Subcommittee considered that the additional supplier-provided evidence was of poor quality and was insufficient to amend its previous recommendation. The Subcommittee reiterated that publication of longer follow-up including mature survival data from the AURA3 trial was awaited (both items of correspondence and the meeting record excerpt are available in **Appendix 1**).

The supplier provided PHARMAC staff with a conference abstract and presentation of the final overall survival AURA3 results, as well as an updated clinical study overview in June 2020, and indicated that the full publication of AURA3 results was expected late 2020. In August 2020, PTAC reviewed this updated information and recommended that osimertinib for the second-line treatment of EGFRm NSCLC be deferred, pending publication and peer-review of the AURA-3 overall survival results (AURA3 materials and record excerpt available in **Appendix 1**)

In 2021, PHARMAC staff identified a new peer-reviewed publication of overall survival outcomes from the AURA3 trial and two other publications from the trial. The supplier has confirmed that this is the final overall survival analysis of AURA3, and no other relevant publications from AURA3 are available. In light of this new published evidence, PHARMAC staff are bringing this application to CaTSoP for further clinical advice.

Evidence Summary

AURA-3 trial

The key clinical evidence for osimertinib in the second-line, EGFR T790M positive NSCLC indication comes from the open-label, randomised, international, AURA3 trial:

> *A phase III, open label, randomised study of AZD9291 versus platinum-based doublet chemotherapy for 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* (**AURA3**; NCT02151981).

For inclusion in the AURA3 trial, the documented presence of an EGFR mutation and central confirmation of the T790M variant on the cobas EGFR Mutation Test (Roche Molecular Systems) after first-line EGFR-TKI treatment was required. All patients were required to

provide a blood sample at screening to test for T790M in plasma circulating tumour DNA (ctDNA) on the cobas EGFR Mutation Test, version 2.

Patients with stable, asymptomatic CNS metastases that had not been treated with glucocorticoids for at least 4 weeks before the first dose of a trial drug were eligible.

Randomisation was 2:1 and patients were stratified according to Asian or non Asian race.

Study endpoints were:

The primary efficacy end point was the duration of investigator-assessed progression-free survival (PFS) according to RECIST v1.1; a sensitivity analysis of PFS by blinded independent central review was conducted.

- Secondary objectives included: response rate per investigator assessment, response duration, disease control rate, tumour shrinkage, **overall survival (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.

A protocol amendment in December 2014 allowed patients who had been assigned to receive platinum-pemetrexed to cross over to the osimertinib group after objective disease progression (per investigator assessment, confirmed by blinded independent central review).

AURA3 trial participant demographics, shown over page in **Figure 2**, were reported in the 2017 publication that was reviewed by CaTSoP in April 2018 (Mok et al. N Engl J Med. 2017;376:629-40).

Figure 2: Demographic and clinical characteristics of AURA3 patients at baseline (Mok et al, 2017).

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Osimertinib (N=279)	Platinum–Pemetrexed (N=140)
Median age (range) — yr	62 (25–85)	63 (20–90)
Female sex — no. (%)	172 (62)	97 (69)
Race — no. (%)†		
White	89 (32)	45 (32)
Asian	182 (65)	92 (66)
Other	8 (3)	3 (2)
No history of smoking — no. (%)	189 (68)	94 (67)
Disease classification — no. (%)		
Adenocarcinoma histology not otherwise specified	232 (83)	122 (87)
Metastatic disease	266 (95)	138 (99)
CNS metastases‡	93 (33)	51 (36)
Extrathoracic visceral metastases§	145 (52)	80 (57)
Type of *EGFR* mutation — no. (%)¶		
T790M‖	275 (99)	138 (99)
Exon 19 deletion	191 (68)	87 (62)
Exon 21 L858R	83 (30)	45 (32)
G719X	4 (1)	2 (1)
S768I	1 (<1)	1 (1)
Exon 20 insertion	1 (<1)	2 (1)
No. of previous anticancer regimens for advanced disease — no. (%)**		
1	269 (96)	134 (96)
2	9 (3)	6 (4)
3	1 (<1)††	0
Previous EGFR-TKI therapy — no. (%)	279 (100)	139 (99)
Gefitinib	166 (59)	87 (62)
Erlotinib	96 (34)	49 (35)
Afatinib	20 (7)	4 (3)

* CNS denotes central nervous system, EGFR epidermal growth factor receptor, and TKI tyrosine kinase inhibitor.
† Race was self-reported. The category of "other" includes black, American Indian, and Alaska Native.
‡ CNS metastases were determined from baseline data for the CNS lesion site, medical history, surgery, or radiotherapy. One patient was identified as having locally advanced disease in the brain.
§ Extrathoracic visceral metastases were determined on the basis of baseline data for which the disease site was described as adrenal, ascites, brain or CNS, gastrointestinal, genitourinary, hepatic (including gallbladder), liver, other CNS, pancreas, peritoneum, or spleen. Also included were other metastatic sites, such as those occurring in the eye and thyroid, as identified as extrathoracic visceral sites by AstraZeneca physicians.
¶ *EGFR* mutations were identified by means of the cobas EGFR Mutation Test from a biopsy sample obtained after confirmation of disease progression while the patient was receiving the most recent treatment regimen.
‖ Six patients (four in the osimertinib group and two in the platinum–pemetrexed group) did not have centrally confirmed T790M mutation–positive status that was documented in the trial database. Three patients (two in the osimertinib group and one in the platinum–pemetrexed group) were subsequently found to have positive results on testing for the T790M mutation. Therefore, three patients (two in the osimertinib group and one in the platinum–pemetrexed group) were T790M-negative in the tumor sample and underwent randomization in error. One of the three patients who had T790M-negative results in the tumor sample had T790M-positive results in plasma.
** Patients were classified as having received more than one previous line of therapy if they received any of the following: adjuvant or neoadjuvant chemotherapy administered less than 6 months before the start of EGFR-TKI therapy; more than one EGFR-TKI (switching from a first-generation EGFR-TKI to a second-generation EGFR-TKI, or restarting EGFR-TKI after >12 months off treatment) administered sequentially; or the addition of anticancer agents such as cytotoxic chemotherapy or a c-Met monoclonal antibody toward the end of a previous monotherapy EGFR-TKI regimen.
†† One patient in the osimertinib group was treated with fulvestrant followed by letrozole before starting EGFR-TKI.

Evidence that was previously reviewed by CaTSoP and/or PTAC is not duplicated in this paper; please refer to the previous clinical advice papers and meeting record excerpts in Appendix 1 for past evidence.

New evidence

A summary of the new, most relevant AURA3 trial publications including overall survival results are provided in the table below (**Table 3**). The supplier has confirmed that the paper by Papadimitrakopoulou et al. (Ann Oncol. 2020) provides the final overall survival analysis for AURA3.

The full-text publications, in addition to the Supplementary Materials document (including statistical analyses for planned OS analysis, OS subgroup analyses and crossover-adjusted OS analysis) and Supplementary Figure S1 (both from Papadimitrakopoulou et al. Ann Oncol. 2020) are available in **Appendix 3**.

In addition, the supplier has provided evidence from a phase I study of osimertinib in patients with EGFRm positive NSCLC with leptomeningeal metastases whose disease has progressed on prior EGFR-TKI therapy (Yang et al. J Clin Oncol. 2020;38:538-47). PHARMAC staff note that this study included a small number (N=20) of patients with T790M mutation positive disease. While potentially less relevant, this is provided in **Appendix 3**.

Table 3: Summary of new evidence for osimertinib for the second-line treatment of EGFR T790M positive NSCLC.

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety (if reported)	Citation
AURA 3	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	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%). Overall survival (OS) secondary endpoint: 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

Trial	Study Design	Patients Group(s)	No. Patients	Intervention	Duration	Efficacy	Safety (if reported)	Citation
AURA 3	AURA3 – CNS efficacy of osimertinib	AURA3 as above Measurable/non-measurable CNS metastases in 116; 46 measurable.	AURA3 as above	AURA3 as above	As above	Data cutoff 15 April 2016. Median CNS progression-free survival: 11.7 months osimertinib vs 5.6 months platinum-pemetrexed (HR, 0.32; 95% CI 0.15 to 0.69; *P*=0.004). Objective response rate (ORR): • ≥1 measurable lesion: 21/30 (70%; 95% CI 51% to 85%) osimertinib vs 5/16 (31%; 95% CI 11% to 59%) platinum-pemetrexed (*P*=0.015). Measurable/non-measurable CNS lesions: 30/75 (40%, 95% CI 29% to 52%) osimertinib vs 7/41 (17%, 95% CI 7% to 32% platinum-pemetrexed (OR, 3.24; 95% CI, 1.33 to 8.81; *P*=0.014)		Wu et al. J Clin Oncol. 2018;36:2702-9
AURA 3	AURA3 – patient reported outcomes	AURA3 as above	AURA3 as above	AURA3 as above	QLQ-LC13 at baseline, weekly for 6 weeks, then 3-weekly until end of study and at progression; QLQ-C30 at baseline then 6-weekly until end of study and at progression.	Baseline completion 82%-88%; scores balanced; ~50%-70% of patients with a key lung cancer symptom. Completion rates (both arms) ≥60% at Y1. Key symptoms incl. dyspnoea (OR, 2.71, 95% CI: 1.60 to 4.38, *P*<0.001), fatigue (OR, 1.96, 95% CI: 1.20 to 3.22, *P*=0.008), appetite loss (OR, 2.50, 95% CI: 1.31 to 4.84, *P*=0.006) improved with osimertinib. Time to deterioration of symptoms prolonged with osimertinib incl. cough (HR, 0.74; 95% CI, 0.53 to 1.05, *P*=0.090), chest pain (HR, 0.52, 95% CI: 0.37 to 0.73, *P*<0.001), dyspnoea (HR, 0.66, 95% CI: 0.47 to 0.91, P=0.11) and appetite loss (HR, 0.46, 95% CI: 0.32 to 0.67 *P*<0.001). Differences in means of symptoms and change in function scores between arms considered to reach thresholds for minimal important differences for improvement.		Lee et al. J Clin Oncol. 2018;36:1853-60

AEs, adverse events; CI, confidence interval; HR, hazard ratio; OR, odds ratio; RPSFTM, rank preserving structural failure time model; QLQ-C30, 30-item Core Quality of Life Questionnaire; QLQ-LC13; 13-item Quality of Life Questionnaire-Lung Cancer Module.

Literature search

During preparation of this paper, PHARMAC staff also identified the following potentially relevant publications reporting outcomes from the AURA3 trial:

- A sub-analysis that evaluated the safety and efficacy of osimertinib in 63 Japanese patients enrolled in AURA3, reporting outcomes that were consistent with the overall AURA3 study (Akamatsu et al. Cancer Sci. 2018;109:1930-8).

  A study assessing different technologies used for detecting EGFR mutations from circulating tumour DNA in AURA3 participants with EGFR T290M-positive NSCLC. With cobas EGFR Mutation Test results (screening tumour tissue biopsy samples) as a reference, the plasma T790M positive percent agreement was 51% (110 of 215 samples) by cobas EGFR Mutation Test v2, 58% (110 of 189) by droplet digital polymerase chain reaction (ddPCR; Biodesix), and 66% (136 of 207) by next-generation sequencing (NGS; Guardant360, Guardant Health) (Papadimitrakopoulou et al. Cancer. 2020;126:373-80).

These publications are also available in **Appendix 3**. A structured literature search regarding osimertinib in other trials and other settings has not been conducted by PHARMAC staff at this time.

International recommendations

Table 4: International recommendations regarding the funding of osimertinib for the second-line (2L) treatment of EGFR T790M mutation positive NSCLC

Country (HTA Agency)	Meeting/ Recommendation Date	Outcome	Reason(s)
Australia (PBAC)	November 2018	✓ The PBAC recommended osimertinib for 2L treatment of EGFR T790M mutation positive locally advanced or metastatic NSCLC	- For some patients, a significant improvement in efficacy and a reduction in toxicity over platinum-based doublet chemotherapy. - Acceptable cost-effectiveness at the capped cost per patient. - Strong support from consumers and the MOGA for osimertinib. - Unmet clinical need for treatment options as patients with EGFR mutation positive NSCLC develop acquired resistance to first-line EGFR TKI therapy.
Canada (CADTH -	May 2017	✓ The CADTH recommended osimertinib for 2L treatment of	Based on net clinical benefit of osimertinib ie a substantial,

Country (HTA Agency)	Meeting/ Recommendation Date	Outcome	Reason(s)
CDEC)		EGFR T790M mutation positive locally advanced or metastatic NSCLC	statistically significant and clinically meaningful improvement in PFS, with a manageable toxicity profile and no change in quality of life. Conditional on cost-effectiveness being improved to an acceptable level.
Scotland (SMC)	February 2017	✓ The SMC recommended osimertinib for locally advanced or metastatic EGFR T790M mutation-positive NSCLC in patients who have received previous treatment with an EGFR TKI (assessed under the ultra orphan and end of life process)	Osimertinib was associated with an overall response rate of 66% in the pooled analysis of two phase II single-arm studies of patients with EGFR T790M advanced NSCLC who had received previous treatment with an EGFR TKI. SMC advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of osimertinib, and views from a Patient and Clinician Engagement (PACE) meeting.
England and Wales (NICE)	October 2020	✓ The NICE recommended osimertinib for epidermal growth factor receptor (EGFR) T790M mutation-positive locally advanced or metastatic non-small-cell lung cancer (NSCLC) in patients whose disease progressed after first-line treatment with an EGFR TKI and the company provides osimertinib according to the commercial arrangement.	Clinical trial evidence suggests that people who take osimertinib live longer than those who have platinum-doublet chemotherapy, although there is some uncertainty about the results. Osimertinib meets NICE's criteria to be considered a life-extending treatment at the end of life. Although the cost-effectiveness estimates for osimertinib are uncertain, they are likely to be within what NICE considers to be an acceptable use of NHS resources.

Costs and Savings

PICO (Population, Intervention, Comparator, Outcome)

Table 5, below, summarises PHARMAC staff's interpretation of the PICO for osimertinib if it were funded in New Zealand for second-line treatment of locally advanced or metastatic NSCLC with EGFRm T790M mutation.

This PICO captures key clinical contexts, helping review the proposal and frame any future economic assessment by PHARMAC. We seek the Subcommittee's advice on the content in the table below.

Note that the PICO may change as clinical and other features evolve.

Table 5: PICO for osimertinib if it were funded in New Zealand for second-line treatment of locally advanced or metastatic NSCLC with EGFRm T790M mutation positive disease.

Population	Patients with locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous Non-Small Cell Lung Cancer (NSCLC), who have the EGFR tyrosine kinase mutation with T790M mutation, and have progressed following first line treatment with a TKI.
Intervention	One osimertinib 80 mg tablet per day until disease progression or unacceptable toxicity. Followed by: 1. Platinum-based chemotherapy 2. Docetaxel (75mg/m^2 3 weekly, 90 min infusion) All therapies taken until disease progression, unacceptable toxicity or death.
Comparator(s) (NZ context)	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(s)	Increase in progression free survival (PFS), increase in overall survival (OS) as described in AURA3.

Table definitions:

Population: The target population for the pharmaceutical, including any population defining characteristics (e.g. line of therapy, disease subgroup)

Intervention: Details of the intervention pharmaceutical (dose, frequency, treatment duration/conditions for treatment cessation).

Comparator: Details the therapy(s) that the patient population would receive currently (status quo – including best supportive care; dose, frequency, treatment duration/conditions for treatment cessation).

Outcomes: Details the key therapeutic outcome(s), including therapeutic intent, outcome definitions, timeframes to achieve outcome(s), and source of outcome data.

Costs and savings to pharmaceutical expenditure

Cost per patient

The supplier recommends the daily dose to be 80 mg (one 80 mg tablet). The price, including a confidential proposed rebate, is S 9(2)(b) (ii) 9(2) for 1 pack containing 30 tablets of 80 mg (30 days' worth at recommended dose). With a median PFS of 10 months reported in the AURA3 trial, the cost per person treated with osimertinib in the second line is estimated to be approximately, S 9(2)(b) (ii) 9(2). PHARMAC staff note that this estimate is based on price

provided by the supplier in the 2019 application for funding in the first line, and that it is possible that a higher price could apply to funding in the second line due to the difference in patient numbers. It should be noted that this would result in a slightly higher budget impact than is currently estimated.

Estimated Incremental Total Cost of Listing

Patient numbers

PHARMAC staff estimate that 66-82 patients a year would be eligible for treatment with osimertinib if it were funded for patients with EGFRm and T790M mutation positive NSCLC, following disease progression on a TKI. The following assumptions were considered in this estimation:

- PHARMAC's dispensing data suggests that the current incidence of patients with EGFRm NSCLC using TKIs first line is approximately 150 patients S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) (source: supplier application). Note: PHARMAC staff note the uncertainty in this assumption, given the uncertainty in the proportion of people who would be biopsied and whether mutation detection though a blood test is possible. This assumption will be updated following clinical advice.

- The supplementary appendix S2 of the AURA3 trial states that, of the 648 patients with plasma ctDNA analysis, 55% (359 patients) tested positive for T790M mutation, 32% (205 patients) tested negative and the remaining 13% (84 patients) were excluded due to invalid plasma results/valid plasma test result but no or invalid tumour test result. Based on this, PHARMAC staff estimate that between 55% and 68% of patients could be expected to test positive for T790M mutation after progression on a TKI.

PHARMAC staff seek the Subcommittee's advice on whether the eligible patient numbers estimated by PHARMAC staff are reasonable.

Further advice from the Subcommittee is also sought regarding uptake as well as the presence and magnitude of a prevalent population with EGFRm T790M mutation positive NSCLC who would be eligible for at the time of funding.

Incremental cost of the listing

A rapid budget impact analysis conducted by PHARMAC staff is presented below for indicative purposes only. The analysis considers the patient numbers estimated by the supplier for the first five years of listing (including a prevalent bolus of S 9(2) patients) and considers the net pharmaceutical cost if each patient was to receive 10 months of treatment (based on the median PFS in AURA3).

PHARMAC note a subsequent BIA including pharmacy margins, the cost of mutation testing and any relevant changes in disease management costs may be conducted following CaTSoP advice. The budget impact below includes consideration of a prevalent patient bolus of S 9(2) people.

Table 6: Budget impact analysis for osimertinib if it were funded in New Zealand for second-line treatment of locally advanced or metastatic NSCLC with EGFRm T790M mutation positive disease.

Year	1	2	3	4	5	NPV*
Patient Numbers	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Net cost to the CPB ($million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
* 8% discount rate annually						

Costs and savings to the rest of the health system

Mutation testing

The funding of osimertinib for the patient population with T790M mutation positive disease may result in the need for an additional biopsy and additional mutation test. PHARMAC note that the supplier has indicated that this would be additional, however, advice received from an Auckland Oncologist (see **Appendix 1**) indicates that clinicians in Auckland routinely re biopsy patients who have received erlotinib or gefitinib at disease progression (if safe to do so) and test the tissue sample for the T790M mutation. This additional biopsy and tumour testing is done so that patients can potentially access unfunded treatments like osimertinib via clinical trials, compassionate access programmes or self-funding. The additional test uses the same assay that is used for EGFR mutation testing at diagnosis.

According to the clinician correspondence, plasma circulating tumour DNA assays for T790M mutation are not currently funded or performed onsite, but are considered reliable, advantageous for treatment decisions, and may be useful for patients who cannot be safely biopsied at disease progression.

PHARMAC staff seek the Subcommittee's advice on:

The current status of T790M testing for NSCLC across New Zealand (including timing and type of test, accuracy, and any additional requirements eg re-biopsy); and

- *Advice regarding additional testing requirements if osimertinib were funded in this setting (eg an additional biopsy and T790M test, and/or testing for plasma circulating DNA; timing of additional tests).*

Disease management and subsequent treatment lines

The funding of osimertinib for the patient population with T790M mutation positive disease would likely delay the use of subsequent lines of therapy, as opposed to replacing therapies.

PHARMAC staff seek the Subcommittee's advice on the magnitude and materiality of changes to disease management and subsequent treatment lines, including any changes resulting from T790M mutation testing, if osimertinib were to be funded.

Cost Effectiveness (combining the Health Benefits and Costs quadrants)

The original supplier application included a model that evaluated the cost-effectiveness of second-line treatment with osimertinib in comparison to platinum-doublet chemotherapy to be approximately S 9 QALYS per million dollars spent. However, PHARMAC staff note that this model has several limitations including that the health system costs have not been updated from United Kingdom based cost to New Zealand health system costs, that the

subsequent lines of treatment modelled appear to include nivolumab which is not funded in New Zealand, and that the model does not incorporate the recent overall survival data from AURA3 which is currently estimated in the model via an indirect comparison.

PHARMAC staff may conduct an assessment of osimertinib in the New Zealand context that reflects currently available evidence, following a recommendation from CaTSoP.

Osimertinib has been reviewed or reviewed by several other health technology assessment bodies since CaTSoP first reviewed this application. An updated summary is provided below.

England and Wales (NICE)

The updated consideration of osimertinib for the proposed indication is summarised in TA653 which was published on October 2020. NICE recommended that osimertinib be funded as an "option for treating epidermal growth factor receptor (EGFR) T790M mutation-positive locally advanced or metastatic non small-cell lung cancer (NSCLC) in adults, only if their disease has progressed after first-line treatment with an EGFR tyrosine kinase inhibitor and the company provides osimertinib according to the commercial arrangement".

In its review, NICE noted the high health need of these patients, the uncertainty in overall survival estimates and uncertainty in health utility, in particular, whether the evidence provided was sufficient to support a treatment-related quality of life improvement while in a PFS state. In terms of the OS benefit, they noted that real-world data from the Cancer Drug Fund for this treatment regimen demonstrated shorter durations of overall survival than in the clinical trials, the published OS estimates in AURA3 were not statistically significant, and that the OS benefit should be adjusted to reflect treatment switching. The committee concluded that a plausible cost-effectiveness range was from 10-12 QALYS per million (NZD) spent.

Australia (PBAC)

Australia revisited the application to fund osimertinib for the proposed indication in November 2018 after rejecting it in November 2017 and subsequently deferring it in July 2018. The defer recommendation in July 2018 acknowledged the clinical benefit osimertinib treatment provided for some patients in terms of PFS and treatment safety, but noted the uncertainty of the magnitude of overall survival benefit from the evidence available. They acknowledged the applicant's efforts to include updated OS data into the economic model and adjust for treatment cross-over. The cost-effectiveness was noted to be between 9-12 QALYs per million dollars (NZD) spent. In their November 2018 review, PBAC noted that the applicant's commercial offer (capped cost per patient) made the cost-effectiveness acceptable.

Canada (CADTH)

CADTH's Pan-Canadian Oncology Drug Review published a review in May 2017. They recommended that osimertinib be funded for this patient group providing the cost-effectiveness could be improved to an acceptable level. The review stated "….the Committee was confident of the net clinical benefit of osimertinib based on a substantial improvement in PFS what was statistically significant and clinically meaningful. Osimertinib also had a manageable toxicity profile and, based on the available data, treatment did not result in a decrement or an improvement in patients' quality of life". In reviewing the submitted economic model, the review noted the limitation relating to the immaturity of OS

data and the uncertainty of benefit post disease progression in terms of the number of people who would receive subsequent treatment and their response.

APPENDICES

Appendix 1: Clinical advice papers and record excerpts:

- CaTSoP April 2018 - Clinical advice paper, appendices & record excerpt
- July 2018 – AstraZeneca correspondence
- August 2018 – Auckland Oncologist correspondence
- CaTSoP September 2018 Record excerpt
- June 2020 - AstraZeneca correspondence and new AURA3 materials
- PTAC August 2020 Clinical advice paper, appendices & record excerpt

Appendix 2: New first-line evidence/information seen by PBAC:

- Gray et al. Clin Cancer Res. 2019;25:6644-52
- Planchard et al. Ann Oncol. 2018;29(Supplement 9):ix150-169

Appendix 3: New evidence/information from AURA-3 trial:

- Papadimitrakopoulou et al. Ann Oncol. 2020;31:1536-44
- Supplementary Materials document (Papadimitrakopoulou et al. Ann Oncol. 2020)
- Supplementary Figure S1 (Papadimitrakopoulou et al. Ann Oncol. 2020)
- Wu et al. J Clin Oncol. 2018;36:2702-9
- Lee et al. J Clin Oncol. 2018;36:1853-60
- Akamatsu et al. Cancer Sci. 2018;109:1930-8
- Papadimitrakopoulou et al. Cancer. 2020;126:373-80
- Yang et al. J Clin Oncol. 2020;38:538-547

THE FACTORS FOR CONSIDERATION

Factors are presented here in the order they appear in the paper, without implying any ranking or relative importance.

NEED

- The health need of the person
- The availability and suitability of existing medicines, medical devices and treatments
- The health need of family, whānau, and wider society
- The impact on the Māori health areas of focus and Māori health outcomes
- The impact on the health outcomes of population groups experiencing health disparities
- The impact on Government health priorities

HEALTH BENEFITS

- The health benefit to the person
- The health benefit to family, whānau and wider society
- Consequences for the health system

SUITABILITY

- The features of the medicine or medical device that impact on use by the person
- The features of the medicine or medical device that impact on use by family, whānau and wider society
- The features of the medicine or medical device that impact on use by the health workforce

COSTS AND SAVINGS

- Health-related costs and savings to the person
- Health-related costs and savings to the family, whānau and wider society
- Costs and savings to pharmaceutical expenditure
- Costs and savings to the rest of the health system

Record of the Cancer Treatment Subcommittee of PTAC Meeting held on 12 April 2021

Cancer Treatment Subcommittee records are published in accordance with the Terms of Reference for the Pharmacology and Therapeutics Advisory Committee (PTAC) and PTAC Subcommittees 2016.

Note that this document is not necessarily a complete record of the Cancer Treatment Subcommittee meeting; only the relevant portions of the meeting record relating to Cancer Treatment Subcommittee discussions about an application or Pharmac staff proposal that contain a recommendation are generally published.

The Cancer Treatment Subcommittee may:

(a) recommend that a pharmaceutical be listed by Pharmac on the Pharmaceutical Schedule and the priority it gives to such a listing;

(b) defer a final recommendation, and give reasons for the deferral (such as the supply of further information) and what is required before further review; or

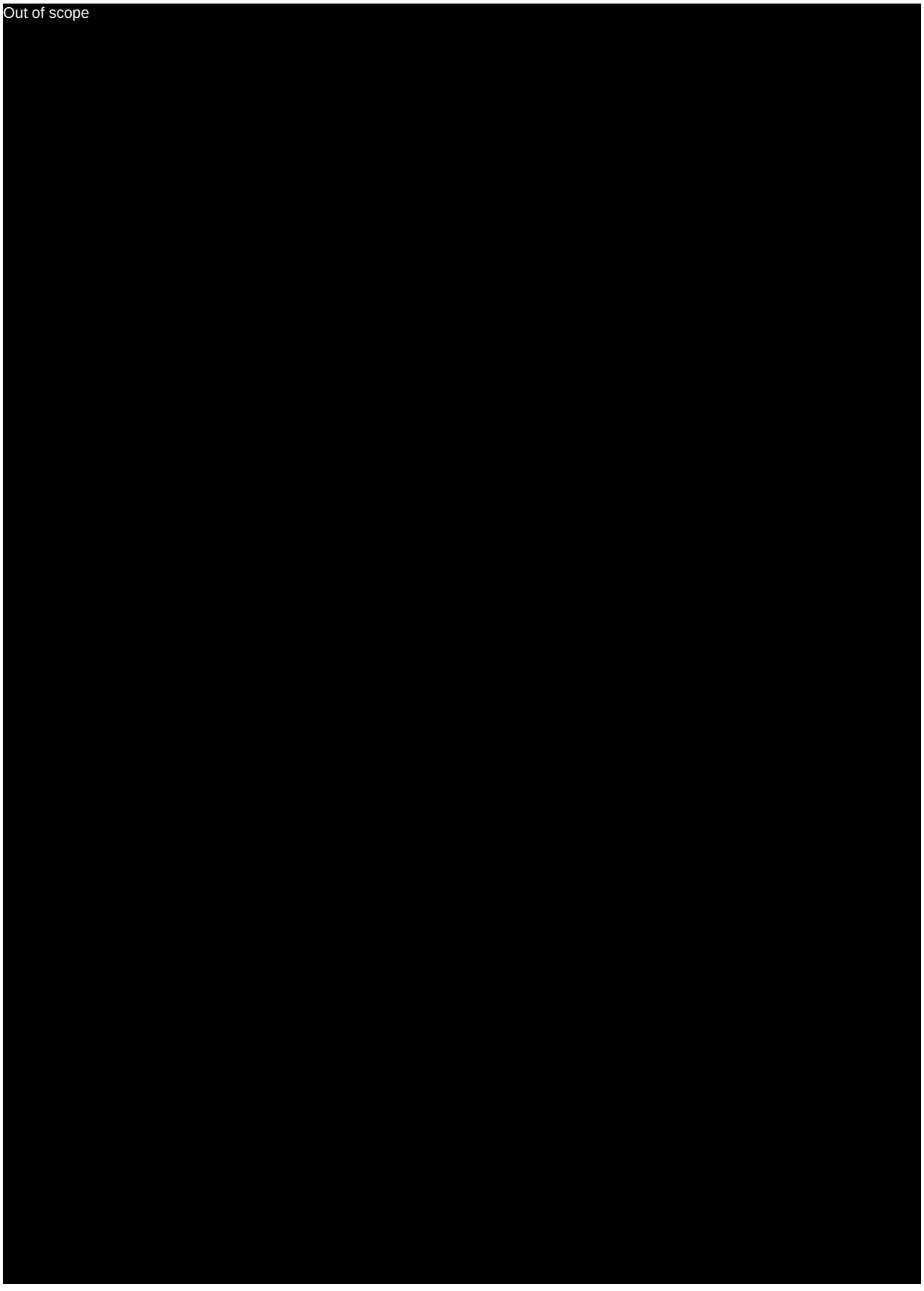
(c) recommend that Pharmac decline to list a pharmaceutical on the Pharmaceutical Schedule.

PTAC Subcommittees make recommendations, including priority, within their therapeutic groups of interest.

The record of this Subcommittee meeting will be reviewed by PTAC at its August 2021 meeting.

PTAC Subcommittees and PTAC may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, if complementary, roles, expertise, experience, and perspectives.

Pharmac is not bound to follow the recommendations made below. Applications are prioritised by Pharmac against other funding options and progressed accordingly. The relative priority of any one funding choice is dependent on a number of factors, including (but not limited to) the recommendation of PTAC and/or PTAC Subcommittees, the mix of other applications being assessed, the amount of funding available, the success of commercial negotiations and/or the availability of clinical data.



7. Osimertinib for the treatment of EGFRm positive non-small cell lung cancer (NSCLC)

Application

7.1. The Subcommittee considered the following applications:

7.1.1. Osimertinib for the first-line treatment of locally advanced or metastatic Epidermal Growth Factor Receptor mutation (EGFRm) positive non-small cell lung cancer (NSCLC), following review of this application by PTAC; and

7.1.2. Osimertinib for the second-line treatment of EGFR T790M mutation-positive NSCLC after prior EGFR tyrosine kinase inhibitor (TKI) therapy, in light of updated evidence from the AURA-3 trial's final overall survival analysis.

Recommendation

7.2. The Subcommittee **recommended** that the application for osimertinib for the first-line treatment of locally advanced or metastatic epidermal growth factor receptor mutation (EGFRm) positive non-small cell lung cancer (NSCLC) be funded with a **high priority**, in the context of treatment of malignancy, subject to the following Special Authority criteria:

OSIMERTINIB
Special Authority for Subsidy – Retail Pharmacy - Specialist
Initial application – (NSCLC – first line) only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Patient has locally advanced (Stage IIIb) or metastatic (Stage IV), non-squamous Non-Small Cell Lung Cancer (NSCLC); and
2. Either
   - 2.1 Patient is treatment naïve; or
   - 2.2 Both:
     - 2.2.1 The patient has discontinued gefitinib or erlotinib due to intolerance; and
     - 2.2.2 The cancer did not progress while on gefitinib or erlotinib; and
3. There is documentation confirming that the disease expresses activating mutations of EGFR tyrosine kinase; and
4. Treatment must be used as monotherapy; and
5. Patient has an ECOG performance status of 2 or less

Renewal - only from a relevant specialist or any other medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

7.2.1. In making this recommendation, the Subcommittee considered the health need of patients with EGFRm positive NSCLC and the evidence supporting an overall survival (OS) benefit with osimertinib compared to first-generation tyrosine kinase inhibitors (TKIs) following long term follow-up, in a comparable patient population.

7.3. The Subcommittee **recommended** that the application for osimertinib for the second-line treatment of epidermal growth factor receptor mutation (EGFRm) T790M mutation-positive non-small cell lung cancer (NSCLC) after prior EGFR tyrosine kinase inhibitor (TKI) therapy be funded with a **high priority**, in the context of treatment of malignancy, subject to the following Special Authority criteria:

OSIMERTINIB
Special Authority for Subsidy – Retail Pharmacy - Specialist

Initial application - (NSCLC – second line) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 4 months for applications meeting the following criteria:
All of the following:

1. Patient has locally advanced or metastatic non-small cell lung cancer; and
2. Patient has an ECOG 0-1; and
3. The patient must have received previous treatment with erlotinib or gefitinib; and
4. There is documentation confirming that the disease expresses T790M mutation of the EGFR gene following progression on or after erlotinib or gefitinib; and
5. The treatment must be given as monotherapy for a maximum of 3 months.

Renewal – (NSCLC) only from a relevant specialist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months where radiological assessment (preferably including CT scan) indicates NSCLC has not progressed.

7.4. In making this recommendation, the Subcommittee considered: the health need of patients with EGFR T790M mutation-positive NSCLC; the evidence of a progression free survival (PFS) benefit with osimertinib in the second-line for EGFR T790M mutated NSCLC and supporting evidence of an OS benefit from osimertinib second-line in a comparable population, and the suitability of osimertinib compared with systemic chemotherapy.

Background

7.5. The Subcommittee noted that the application for osimertinib for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC was considered by PTAC in August 2020. At that time, PTAC recommended it be funded if cost-neutral to current first-line TKI's, erlotinib and/or gefitinib, due to:

- 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; and
- The high quality, randomised-control trial evidence that reported benefit in progression free survival compared with the comparator (gefitinib or erlotinib); and
- The uncertain evidence regarding benefit in overall survival compared with the comparator (erlotinib or gefitinib); and
- The lack of evidence of superiority of osimertinib to the current two first-line pharmaceuticals for this indication.

7.5.1. At that time, PTAC considered that Pharmac could seek advice from CaTSoP regarding the sequence of treatments in this indication, and appropriate Special Authority criteria for osimertinib in the first-line setting.

7.6. The Subcommittee noted that the application for osimertinib for second-line treatment of EGFR T790M mutation-positive NSCLC after prior EGFR TKI therapy was received in November 2017 and was considered by CaTSoP in April 2018 with a recommendation to defer pending publication of longer-term follow-up data including mature survival data from the AURA-3 clinical trial.

7.6.1. The Subcommittee noted that Pharmac received correspondence from the supplier, AstraZeneca, and from clinicians regarding osimertinib, which was subsequently considered by CaTSoP in September 2018 and reiterated that publication of longer-term mature survival data (including AURA-3 trial data) was awaited.

7.6.2. The Subcommittee noted that updated AURA-3 study materials provided by the supplier in June 2020 were considered by PTAC in August 2020, where it was recommended that the application be deferred pending publication and peer-review of AURA-3 overall survival results.

7.6.3. The Subcommittee noted that in early 2021, a peer-reviewed publication of overall survival outcomes from the AURA-3 trial and two other publications from the trial were made available warranting further consideration of the application.

Discussion

7.7. PTAC and PTAC Subcommittees may differ in the advice they provide to Pharmac, including recommendations' priority, due to the committees' different, albeit complementary, roles, expertise, experience, and perspectives.

7.8. The Subcommittee noted that 90% of lung cancers diagnosed in New Zealand are non-small cell lung cancer (NSCLC) and that EGFRm positive disease has been estimated to occur in about 20% of NSCLC, equivalent to 91 new registrations in Māori and 337 in non-Māori based on 2018 data (Ministry of Health, 2018). The Subcommittee considered the health need of patients with NSCLC is well documented in previous CaTSoP and PTAC records and that the content of those records remains accurate in this regard.

7.9. The Subcommittee noted that international treatment guidelines recommend molecular testing for all patients with metastatic non-squamous lung cancer to identify potential therapeutic targets. The Subcommittee noted that approximately 65% of New Zealand patients with NSCLC received EGFR mutation testing in 2014 leading to an estimated prevalence of EGFRm positive disease of approximately 15.5% if all patients with NSCLC were tested (Tin Tin et al. Cancer Epidemiol. 2018;57:24-32).

7.10. The Subcommittee noted that mutation testing currently uses tumour tissue based samples, however, members considered that about 15-25% of patients may not be physically able to undergo the biopsy procedure required. The Subcommittee noted that liquid (blood) based testing is currently undertaken internationally and within some New Zealand centres, using circulating tumour DNA (ctDNA) typically via either private funding or as part of a clinical trial. The Subcommittee noted that some laboratories are developing their own assays, however, access to biopsies and testing is variable.

7.11. The Subcommittee considered the capability to undertake ctDNA testing consistently throughout New Zealand without the requirement for tissue biopsy would enable a greater number of patients to be tested for EGFR mutations. Members considered that ctDNA testing is likely to be introduced within the next five years and that there would be further evolution of mutation testing in New Zealand to track changes over time. The Subcommittee reiterated its suggestion for Pharmac to engage with laboratory representatives, noting the range of potential EGFR mutations and resistance mechanisms, with complexity and testing likely to increase over time.

7.12. The Subcommittee noted that people with EGFRm positive NSCLC currently receive first-line treatment with erlotinib or gefitinib, followed by second and third-line treatment with platinum-based chemotherapy and docetaxel, respectively. The Subcommittee considered that approximately 60-80% of patients with EGFRm

positive NSCLC respond to first-line treatment with erlotinib or gefitinib (time to progression of between 9.2 to 13.1 months based on Wang et al. Ther Adv Med Oncol. 2012;4:19-29), and approximately 40-60% of these patients will develop T790M mutation (based on Hata et al. Cancer. 2013;119:4325-32 and Chai et al. Cancer Manag Res. 2020;12:5439-50), signalling disease progression and acquired treatment resistance. The Subcommittee noted that there is currently no funded treatment to specifically target T790M mutation positive disease.

7.13. The Subcommittee considered the target EGFRm positive NSCLC population is mutually exclusive to the PD-L1 positive population with NSCLC and funding a new agent in this population would be unlikely to impact the broader funded treatment paradigm for NSCLC. The Subcommittee considered that there is evidence that immune checkpoint inhibitors are not as effective in patients with driver mutations, although the evidence for checkpoint inhibitors and driver mutation targeting agents is evolving.

7.14. The Subcommittee noted that osimertinib is a third-generation tyrosine kinase inhibitor (TKI) that has been investigated for EGFRm positive NSCLC in the phase III FLAURA (first-line osimertinib vs gefitinib or erlotinib) and AURA-3 (second-line osimertinib vs pemetrexed with carboplatin/cisplatin in T790M mutation positive disease) clinical trials. The Subcommittee noted that other third generation TKIs have been unsuccessful in trials therefore osimertinib was the only third generation TKI currently available.

7.15. The Subcommittee was made aware of evidence that, similar to first-generation TKIs, patients inevitably develop resistance to osimertinib either in the first- or second-line setting and considered that this may lead to resistance mechanisms that would either enable subsequent treatment options (eg first-generation TKIs, erlotinib and/or gefitinib) to be effective or render them ineffective (Leonetti et al. Br J Cancer. 2019; 121: 725–37). The Subcommittee considered it was unclear what the impact of these cross-resistant mechanisms would be on usage of erlotinib or gefitinib in the second line.

7.16. The Subcommittee noted that funding agencies in Australia (PBAC), England and Wales (NICE) and Canada (CADTH) have recommended osimertinib be funded in both the first- and second-line settings; however, osimertinib is recommended only as a second line treatment for patients with EGFRm T790M positive NSCLC by the Scottish Medicines Consortium (SMC). The Subcommittee also noted that osimertinib is recommended only as a first-line treatment for EGFRm positive NSCLC by the American Society of Clinical Oncology (ASCO) (Hanna et al. J Clin Oncol. 2021;39:1040-91).

Osimertinib in the first-line

7.17. The Subcommittee noted the application for osimertinib for the first-line treatment of locally advanced or metastatic EGFRm positive NSCLC targeted patients with stage IIIb or stage IV NSCLC who were treatment-naïve or had discontinued treatment with erlotinib/gefitinib due to intolerance (not progression), and who had WHO performance status of two or less.

7.18. The Subcommittee noted the key evidence for osimertinib in this setting comes from the phase III, double-blind, randomised (1:1) controlled FLAURA trial of osimertinib (80 mg once daily) compared with gefitinib (250 mg once daily) or erlotinib (150 mg once daily) in 556 treatment-naïve patients with locally advanced

or metastatic EGFRm positive NSCLC (Soria et al. N Engl J Med. 2018;372:113-25).

7.18.1. The Subcommittee noted that the FLAURA trial population was limited to only a few possible EGFR mutations, was generally well balanced between treatment groups and considered that, although there was a greater proportion of Asian participants than the New Zealand population, the population appeared relevant to the New Zealand context.

7.18.2. The Subcommittee noted that a greater proportion of patients received gefitinib in the comparator group (66%) compared to erlotinib, but considered the inverse to be true for New Zealand standard of care. Members considered, however, that the choice of first generation TKI was unlikely to make a difference in terms of subsequent eligible population, and considered the FLAURA trial comparators were comparable to standard of care.

7.18.3. The Subcommittee noted that the FLAURA trial reported an outcome of median PFS of 18.9 months with osimertinib compared to 10.2 months with the standard TKI comparator (hazard ratio [HR] for disease progression or death 0.46, 95%: CI 0.37-0.57, *P*<0.001) and noted that this PFS benefit of osimertinib compared to first-generation TKIs was statistically significant across all subgroups.

7.18.4. The Subcommittee noted that an updated publication of the FLAURA trial reported median overall survival (OS) of 38.6 months in the osimertinib group compared with 31.8 months in the comparator arm (HR 0.80, 95.05% CI: 0.64-1.00; *P*=0.046) (Ramalingam et al. N Engl J Med. 2020;382:41-50). The Subcommittee considered that the data for up to three years of follow-up indicated a significant benefit in OS from osimertinib compared to first-generation TKIs, noting that a number of patients remained on randomised first-line treatment at three years (78 [28%] in the osimertinib group and 26 [9%] in the comparator group).

7.18.5. The Subcommittee considered that the toxicities reported with osimertinib were as expected for a TKI treatment, and that the trial's secondary endpoints favoured osimertinib treatment.

7.18.6. The Subcommittee noted that 65% of the comparator group received subsequent treatment, with substantial crossover in 47% of these patients receiving osimertinib second line. The Subcommittee considered that the difference in OS seen with osimertinib in the context of this extent of crossover supports the survival benefit of this treatment.

7.19. The Subcommittee considered that first-line osimertinib uptake (compared to erlotinib or gefitinib) would be high and rapid among newly diagnosed EGFRm positive patients, in part due to the ASCO recommendation for its use as first-line treatment in this population. The Subcommittee considered that, based on current access to EGFR testing, approximately 200 patients per year might be eligible for first-line osimertinib treatment. The Subcommittee considered that, as testing becomes more accessible throughout New Zealand there is likely to be a gradual increase in the eligible patient numbers, with further increases once ctDNA testing becomes routinely available (potentially up to approximately 400 per year).

7.20. The Subcommittee considered that, if osimertinib were funded for first-line treatment of EGFRm positive NSCLC, current patients with stable disease on a

first-generation TKI who are not experiencing dose-limiting toxicities would be unlikely to switch to osimertinib. The Subcommittee noted that there was sparse evidence to inform what potential benefit patients who received first-line osimertinib might receive from second-line treatment with first-generation TKIs in the event of disease progression.

7.21. The Subcommittee considered that the Special Authority criteria proposed for first-line osimertinib in this setting, adjusted to align with currently funded TKI criteria and including ECOG rather than WHO performance status, would be appropriate to target funding.

Osimertinib in the second-line

7.22. The Subcommittee noted that the application for osimertinib for the second-line treatment of locally advanced or metastatic EGFRm T790M positive NSCLC targeted patients with stage IIIb or stage IV NSCLC who had progressed following treatment with an EGFR TKI.

7.23. The Subcommittee noted that the key clinical evidence for osimertinib in the second-line for EGFR T790M mutation positive NSCLC comes from the phase III, open-label, randomised (2:1) international, AURA-3 trial which recruited 419 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. The Subcommittee noted that overall survival was a secondary outcome in AURA-3 and that the final overall survival analysis had now been published (Papadimitrakopoulou et al. Ann Oncol. 2020;31:1536-44).

7.23.1. The Subcommittee noted that the cobas EGFR Mutation Test was used to confirm EGFRm and T790M mutation status after progression on a first-line EGFR TKI. The Subcommittee noted that participants were able to be enrolled if they had stable central nervous system metastasis and that there was a high proportion of Asian participants in the trial. Overall, the Subcommittee considered that the trial population and comparator treatments were comparable to the New Zealand setting.

7.23.2. The Subcommittee noted that AURA-3 participants were randomised to receive either 80 mg osimertinib orally once daily or intravenous pemetrexed 500 mg/m2 of body surface area plus either carboplatin (target area under the curve, 5) or 75 mg/m2 cisplatin every 3 weeks for up to six cycles, with or without pemetrexed maintenance, until disease progression or unacceptable toxicity. The Subcommittee noted that cross over to osimertinib was permitted at disease progression for participants in the comparator group.

7.23.3. The Subcommittee noted that the primary outcome of AURA-3 was progression free survival (PFS);;CaTSoP had previously reviewed a publication from AURA-3 with PFS outcomes in April 2018 which reported a benefit with osimertinib across all subgroups (Mok et al. N Engl J Med 2017; 376:629-640). The Subcommittee considered this was good quality evidence of a PFS benefit.

7.24. The Subcommittee noted that overall survival (OS) was a secondary endpoint and that the final OS analysis of AURA-3 after data cut-off (March 2019) reported a median OS of 26.8 months with osimertinib vs 22.5 months with platinum-pemetrexed which was not statistically significant (HR 0.87, 95% CI: 0.67 to 1.12,

P=0.277) (Papadimitrakopoulou et al. Ann Oncol. 2020;31:1536-44). The Subcommittee noted there was substantial crossover from platinum-pemetrexed to osimertinib (N=99; 73% of platinum-pemetrexed group) and considered that while this limited extrapolation of this data to the New Zealand setting, it suggests that osimertinib may be useful in either the second-line or third-line setting.

7.24.1. The Subcommittee noted that the AURA-3 final analysis used a rank preserving structural failure time model (RPSFTM) to report an exploratory crossover-adjusted median OS of 26.8 months with osimertinib vs 15.9 months with platinum-pemetrexed (HR 0.54, 95% CI: 0.18 to 1.60). The Subcommittee noted the wide confidence interval which crossed one, however, members considered that the statistical analysis with this model supports a survival benefit of osimertinib compared with platinum-pemetrexed chemotherapy and highlights the effect of treatment crossover on the results of the non-adjusted OS analysis.

7.24.2. The Subcommittee considered that the methods within the rank preserving structural failure time model (RPSFTM) crossover-adjusted analysis were reasonable and appropriate, and that the results were applicable to the New Zealand context as no third-line EGFR TKIs are available following progression on platinum-pemetrexed chemotherapy. However, the Subcommittee acknowledged that the confidence intervals were wide and that it was not possible to remove or account for all crossover effects. The Subcommittee considered that the evidence for OS was of moderate quality.

7.25. The Subcommittee noted the AURA-3 patient-reported outcomes which identified patients who received osimertinib had 15% better global health-related quality of life (QOL) (OR 2.11, CI 1.24 to 3.67, P=0.007) and increased time to deterioration for chest pain (HR, 0.52, 95% CI: 0.37 to 0.73, P<0.001) and dyspnoea (HR 0.66, 95% CI: 0.47 to 0.91, P=0.11) compared to the comparator (Lee et al. J Clin Oncol. 2018;36:1853-60). The Subcommittee noted that other metrics were not statistically significant but considered that there was a trend towards other improvements in QOL.

7.26. The Subcommittee also noted the following publications:

- Wu et al. J Clin Oncol. 2018;36:2702-9
- Yang et al. J Clin Oncol. 2020;38:538-47
- Akamatsu et al. Cancer Sci. 2018;109:1930-8
- Papadimitrakopoulou et al. Cancer. 2020;126:373-80

7.27. Overall, the Subcommittee considered that there is evidence of a PFS benefit with osimertinib second-line for EGFR T790M mutation-positive NSCLC, and that the post-hoc crossover-adjusted analysis supports an OS benefit in a comparable population.

7.28. The Subcommittee noted that osimertinib offers suitability over systemic chemotherapy due to easier administration and reduced toxicities.

7.29. The Subcommittee considered that most patients who discontinue first-line EGFR TKI treatment would be eligible for second-line treatment, therefore there would be a prevalent pool of patients with EGFR positive NSCLC that would be made up of

approximately 150 patients currently on a 1st generation TKI, and approximately 75 patients who have previously discontinued due to prior disease progression. The Subcommittee considered that uptake would likely be rapid.

7.30. The Subcommittee was made aware of a Canadian publication reporting participation in osimertinib clinical trials which reported that 97.5% of patients who progressed after first-line treatment with a first-generation EGFR TKI had a biopsy at disease progression, with patients typically requiring an average of two biopsies (Chu et al. Curr Oncol. 2020;27:27-33). The Subcommittee considered that in New Zealand, up to five biopsies may be attempted per patient and, based on the Canadian data, almost all of the approximately 150 New Zealand patients receiving an EGFR TKI per year would proceed to a biopsy post-disease progression, of which approximately 109 would have successful biopsies in the first instance.

7.31. The Subcommittee considered that, based on extrapolation of the Canadian trial data, approximately 40-60% of New Zealand patients would test positive for T790M mutation after progression on a TKI (approximately 62 of 109 successfully biopsied patients) which is slightly less than what may be estimated from the AURA-3 trial data alone (from Supplementary appendix S2). The Subcommittee reiterated that implementation of ctDNA testing would increase the number of T790M mutations identified.

7.32. The Subcommittee considered there was a long period of time between progression (occurring after about 10-12 months) and overall survival (about 20 to 30 months) in patients with EGFR positive NSCLC treated with EGFR TKIs or chemotherapy, providing ample opportunity for repeat biopsies if needed for T790M mutation testing (Wang et al. Ther Adv Med Oncol. 2012;4:19-29).

7.33. The Subcommittee noted that a validated, accredited T790M mutation test is not available in New Zealand although there is variable access to T790M testing which may be added into testing performed at some centres. The Subcommittee considered that Pharmac could seek further advice from professional pathology societies in New Zealand such as the Royal College of Pathologists of Australasia (RCPA) to understand testing in the New Zealand context independent of inter-centre variability. The Subcommittee considered that the number of patients who would seek access to funded treatments for T790M positive disease would increase if validated ctDNA testing were implemented and performed routinely in New Zealand.

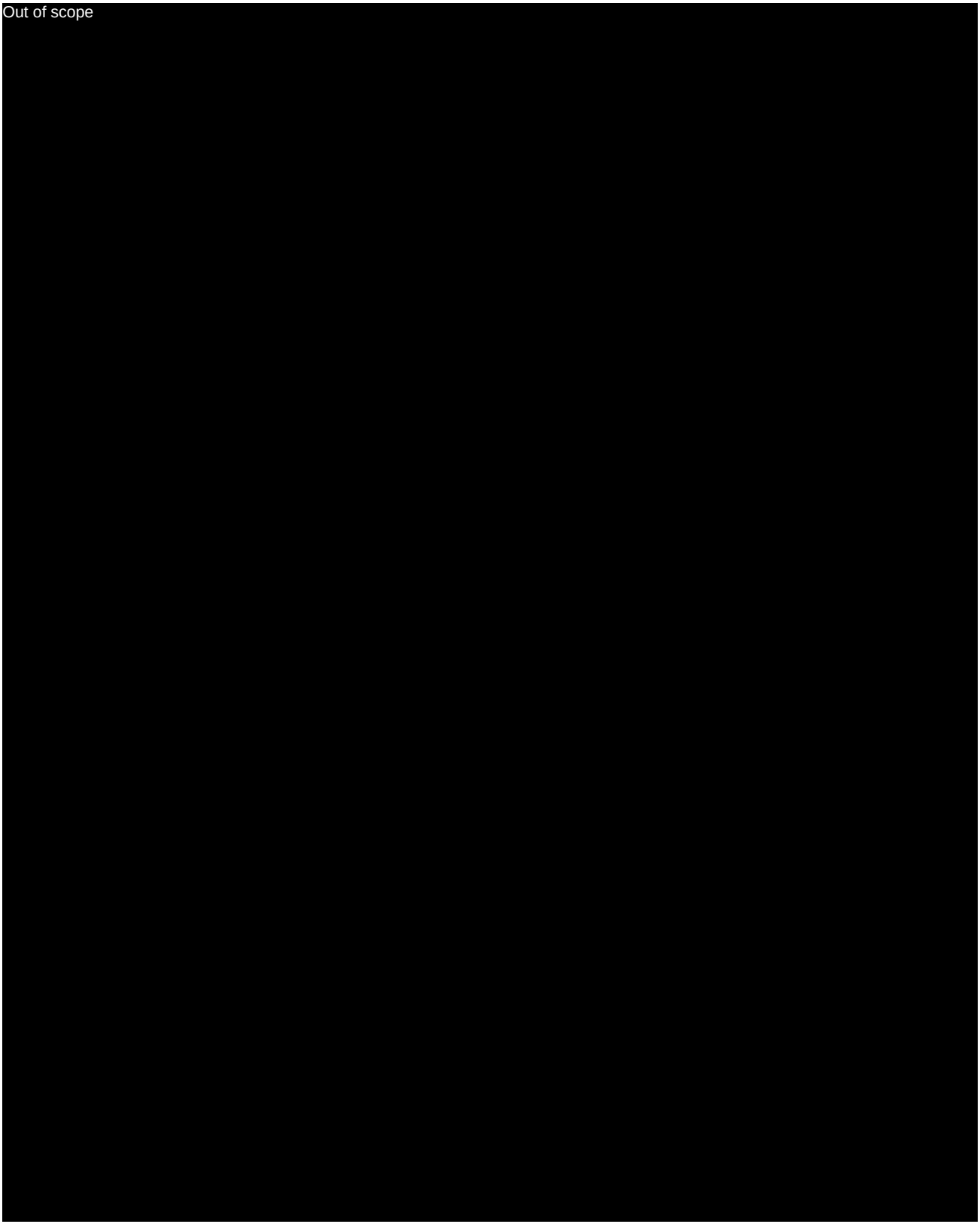
7.34. The Subcommittee considered that funding of osimertinib in the second-line would have additional health system impact for 12- to 18-months due to on-treatment monitoring (monthly clinic visits, three-monthly CT scans, and blood tests), and a small number of patients (approximately <5%, or 3-4 patients per year) who would require hospital admission for management of grade 3-4 adverse events.

7.35. The Subcommittee considered that the proposed Special Authority criteria would appropriately target osimertinib treatment to the population with EGFR T790M mutation positive disease who would benefit in the second-line setting, including patients with central nervous system metastasis. The Subcommittee considered that further evaluation of these may be required if there were to be changes to the evidence regarding immune check point inhibitors in driver mutation NSCLC.

General

7.36. The Subcommittee considered that there was evidence to support benefit from osimertinib in each of the first-line and second-line treatment settings, and supported funding osimertinib for a treatment line, either within first-line or second-line. However, the Subcommittee considered that it was not clinically appropriate for a patient to receive osimertinib in more than one treatment line.

Out of scope



PTAC Pharmacology and Therapeutics Advisory Committee

Objective advice to PHARMAC

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Record of the Pharmacology and Therapeutics Advisory Committee Meeting

Held on 20 & 21 August 2020 via Videoconference

Out of scope

7. Osimertinib for first-line treatment of EGFRm NSCLC

Application

7.1. The Committee reviewed the application for osimertinib for the first-line treatment of locally advanced or metastatic epidermal growth factor receptor mutated (EGFRm) non-small cell lung cancer (NSCLC).

7.2. The Committee also reviewed additional information submitted for the previous 2017 application for osimertinib in the second-line treatment of locally advanced or metastatic EGFRm T790M positive NSCLC.

7.3. The Committee took into account, where applicable, PHARMAC's relevant decision-making framework when considering this agenda item.

Recommendation

7.4. The Committee **recommended** that osimertinib for the first-line treatment of EGFRm NSCLC be funded **if cost-neutral** to current first-line pharmaceuticals in this indication, due to:

- 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; and
- High quality, randomised-control trial evidence that reported benefit in progression free survival compared with the comparator (gefitinib or erlotinib); and
- Uncertain evidence regarding benefit in overall survival compared with the comparator (erlotinib or gefitinib); and
- The lack of evidence of superiority of osimertinib to the current two first-line pharmaceuticals for this indication.

7.5. The Committee considered that PHARMAC could seek subsequent advice from the Cancer Treatments Subcommittee of PTAC (CaTSoP) regarding the sequence of treatments in this indication, and appropriate Special Authority criteria for osimertinib in the first-line setting.

7.6. The Committee **recommended** that osimertinib for the second-line treatment of EGFRm NSCLC be **deferred**, pending publication and peer-review of the AURA-3 overall survival results.

Discussion

Osimertinib in the first-line

7.7. The Committee noted that lung cancer is the leading cause of cancer death in New Zealand. The Committee noted that in New Zealand approximately 89% of lung cancer is non-small cell lung cancer (NSCLC), and 22% of NSCLC patients tested for the Epidermal Growth Factor Receptor mutation (EGFRm) have EGFRm positive tumours. The Committee noted that, in general, Māori are disproportionally impacted by lung cancer compared with non-Māori, with younger age of onset, late diagnosis and worse outcomes. The Committee noted that there is a higher tested and reported incidence of EGFRm in South-East Asian patients (40%) and Pacific patients (24%) than in New Zealand European (18%) or Māori patients (10%) (McKeage et al. Technical report for the Heath Innovation Partnership of the Health Research Council of New Zealand and National Health Committee. 2015).

7.8. The Committee noted that people with lung cancer have a high health need; however, considered that there are inequities in regard to outcomes and available treatment options between lung cancer subgroups. The Committee considered that people with EGFRm NSCLC generally have a longer baseline survival than other subsets of lung cancer. The Committee noted that there are two currently funded first-line tyrosine kinase inhibitors (TKIs) that target EGFR mutations. Members therefore considered that the unmet need for osimertinib in this first-line setting may be lower than in other lung cancer subgroups for which a targeted treatment is not funded.

7.9. The Committee noted that resistance often develops following tyrosine kinase inhibitor (TKI) treatment and that this is most commonly caused by the T790 mutation. The Committee noted that osimertinib is an orally administered third generation TKI that is a selective and irreversible inhibitor of EGFRs harbouring single (L858R or del746-750) or double (L858R/T790M or del746-750/T790M) mutations. The Committee noted that osimertinib has similar side effects to other funded TKIs.

7.10. The Committee noted the results of the FLAURA phase III, double-blind, randomised control trial, which investigated the use of osimertinib compared with gefitinib or erlotinib in patients with locally advanced or metastatic EGFRm NSCLC.

7.10.1. The Committee noted the median progression free survival (PFS) was 18.9 months in the osimertinib group compared with 10.2 months in the comparator group, hazard ratio (HR) for disease progression or death 0.46 (95% confidence interval (CI) 0.37-0.57) (Soria et al. N Engl J Med. 2018;372:113-25).

7.10.2. The Committee noted the secondary outcome of median overall survival (OS) was 38.6 months in the osimertinib group compared with 31.8 months in the comparator arm, HR for death 0.80 (95.05% CI: 0.64-1.00; p=0.046) (Ramalingam et al. N Engl J Med. 2020;382:41-50).

7.10.3. The Committee considered that the trial was of high quality, however that the results for OS were still immature with borderline significance, with the upper confidence interval limit for the HR including 1.00, and noted that the published results attained statistical significance for OS p-values only by extending the HR's CI beyond 95%, which the Committee considered differed from usual formal statistical reporting convention.

7.11. The Committee noted the results of the Japanese subset population of the FLAURA trial (Ohe et al. Jpn J Clin Oncol. 2019;49:29-36). The Committee noted that median PFS was 19.1 months in the osimertinib group compared with 13.8 months in the gefitinib group, HR 0.61 (95% CI 0.38-0.99). The Committee noted that the median OS was not reached.

7.12. The Committee also noted the FLAURA trial publications regarding central nervous system (CNS) progression (Reungwetwattana et al. J Clin Oncol. 2018;36:3290-7), a subset of Asian patients enrolled at Asian sites (Cho et al. J Thorac Oncol. 2019;14:99-106), subsequent treatment (Planchard et al. Clin Cancer Res.2019;25:2058-64), and quality of life (Leighl et al. Eur J Cancer. 2020;125:49-57).

7.13. The Committee considered that while the evidence of osimertinib in this indication was of high quality and reported improved PFS compared with gefitinib/erlotinib, the uncertainty of overall survival benefit of osimertinib over gefitinib/erlotinib and the lower unmet health need of this patient group compared with other lung cancer subtypes influenced the cost-neutral recommendation.

7.14. The Committee noted that NICE (England/Wales) did not recommend osimertinib for untreated locally advanced or metastatic EGFR mutation-positive NSCLC in adults; this lack of a positive recommendation also influenced PTAC's cost-neutral recommendation over a higher positive recommendation. The Committee also noted the PBAC (Australia), CADTH's pERC (Canada) and SMC (Scotland) did not recommend osimertinib for this indication.

7.15. The Committee noted that currently funded first-line treatments for patients with EGFRm NSCLC include the oral TKIs erlotinib and gefitinib. The Committee considered that these agents were appropriate comparators to osimertinib in this treatment line. The Committee considered that while osimertinib had demonstrated efficacy in this patient population, there was no clear unmet health need for a third TKI in the first-line setting for EGFRm NSCLC. The Committee noted that following disease progression on current first-line treatment, second-line treatment is platinum-based doublet chemotherapy.

7.16. The Committee noted that EGFR mutation testing is already occurring for first-line treatment and that this proposal would therefore not result in further mutation testing.

7.17. The Committee noted when making its recommendation that the net price of the two currently funded pharmaceuticals in this line of treatment (erlotinib and gefitinib) may be different and that its cost-neutral recommendation related to cost-neutrality to the more expensive of the two agents. The Committee noted that, were osimertinib to be funded on this basis, that this would likely result in a net increase in expenditure for this line of treatment.

7.18. The Committee considered it was unclear whether targeted treatments would be a suitable option in patients who progressed on osimertinib if used in this first-line setting. The Committee considered that PHARMAC could seek advice from CaTSoP regarding the sequence of treatments in this indication.

7.19. The Committee noted that there are a number of ongoing clinical trials investigating the use of multiple TKIs in combination for the treatment of EGFRm NSCLC. The Committee considered that, pending the results of these trials, there may be requests to PHARMAC for funding of combination TKI treatment over monotherapy in the future.

Osimertinib in the second-line

7.20. The Committee noted that an application for osimertinib in the second-line treatment of EGFRm NSCLC was deferred by the CaTSoP in 2018, pending publication of longer follow-up including mature survival data from the AURA-3 trial (CaTSoP. 2018).

7.21. The Committee reviewed an abstract and conference presentation of the AURA-3 trial overall survival data provided by the supplier. The Committee noted that the results had not been published in a peer reviewed setting at the time of the meeting, and as such deferred making a recommendation on this application pending the availability of peer reviewed published results.

7.21.1. The Committee considered that further information regarding the statistical analysis methodology would be helpful in informing its assessment of the strength and quality of the evidence, including (but not limited to) the cross-over adjustments made and the abstract's intention-to-treat (ITT) analysis reporting apparently no difference in mortality. The Committee considered an assessment of the peer-reviewed data could be completed by PTAC or by CaTSoP.

7.21.2. The Committee considered osimertinib in the second-line setting would require lung re-biopsy, which would be associated with morbidity and mortality risks beyond the disease and potential side effects of the pharmaceutical itself.

Out of scope

[redacted]

ORIGINAL ARTICLE

Osimertinib in Resected *EGFR*-Mutated Non–Small-Cell Lung Cancer

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ABSTRACT

BACKGROUND

Osimertinib is standard-of-care therapy for previously untreated epidermal growth factor receptor (*EGFR*) mutation–positive advanced non–small-cell lung cancer (NSCLC). The efficacy and safety of osimertinib as adjuvant therapy are unknown.

METHODS

In this double-blind, phase 3 trial, we randomly assigned patients with completely resected *EGFR* mutation–positive NSCLC in a 1:1 ratio to receive either osimertinib (80 mg once daily) or placebo for 3 years. The primary end point was disease-free survival among patients with stage II to IIIA disease (according to investigator assessment). The secondary end points included disease-free survival in the overall population of patients with stage IB to IIIA disease, overall survival, and safety.

RESULTS

A total of 682 patients underwent randomization (339 to the osimertinib group and 343 to the placebo group). At 24 months, 90% of the patients with stage II to IIIA disease in the osimertinib group (95% confidence interval [CI], 84 to 93) and 44% of those in the placebo group (95% CI, 37 to 51) were alive and disease-free (overall hazard ratio for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26; P<0.001). In the overall population, 89% of the patients in the osimertinib group (95% CI, 85 to 92) and 52% of those in the placebo group (95% CI, 46 to 58) were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.20; 99.12% CI, 0.14 to 0.30; P<0.001). At 24 months, 98% of the patients in the osimertinib group (95% CI, 95 to 99) and 85% of those in the placebo group (95% CI, 80 to 89) were alive and did not have central nervous system disease (overall hazard ratio for disease recurrence or death, 0.18; 95% CI, 0.10 to 0.33). Overall survival data were immature; 29 patients died (9 in the osimertinib group and 20 in the placebo group). No new safety concerns were noted.

CONCLUSIONS

In patients with stage IB to IIIA *EGFR* mutation–positive NSCLC, disease-free survival was significantly longer among those who received osimertinib than among those who received placebo. (Funded by AstraZeneca; ADAURA ClinicalTrials.gov number, NCT02511106.)

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*A complete list of the ADAURA investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Approximately 30% of patients with non–small-cell lung cancer (NSCLC) present with resectable disease.[1-3] Postoperative adjuvant cisplatin-based chemotherapy is recommended in patients with completely resected stage II to IIIA disease and — subject to postoperative evaluation to assess benefits and risks — in selected patients with stage IB disease. However, this therapy is associated with only a 16% decrease in the risk of disease recurrence or death; at 5 years, it is associated with a 5% decrease in the risk of death.[4,5] Over a median follow-up of approximately 5 years, the percentage of patients who have disease recurrence or who die after surgery remains high (ranging from 45% among patients with stage IB disease to 76% among those with stage III disease), regardless of the use of postoperative chemotherapy.[5]

Epidermal growth factor receptor (*EGFR*) mutations such as exon 19 deletions (Ex19del) and exon 21 codon p.Leu858Arg (L858R) point mutations are common oncogenic driver mutations in NSCLC.[6,7] EGFR tyrosine kinase inhibitors (EGFR-TKIs) are the recommended first-line treatment for *EGFR* mutation–positive advanced NSCLC.[8-13] The efficacy of EGFR-TKIs in patients with advanced disease led to investigation of their use as an adjuvant treatment for resectable disease. Studies have shown that disease-free survival may be longer among patients with resected *EGFR* mutation–positive NSCLC who receive adjuvant first-generation EGFR-TKIs than among those who receive adjuvant chemotherapy or placebo.[14,15]

Osimertinib, a third-generation oral EGFR-TKI, potently and selectively inhibits both EGFR-TKI sensitizing and *EGFR* p.Thr790Met resistance mutations, with efficacy in NSCLC central nervous system (CNS) metastases.[16-20] In the phase 3 FLAURA trial, osimertinib was superior to gefitinib or erlotinib with respect to progression-free and overall survival. These findings provided support for osimertinib as the standard-of-care therapy for previously untreated *EGFR* mutation–positive (Ex19del or L858R) advanced NSCLC.[18,21] Furthermore, the incidence of adverse events of grade 3 or higher among patients who received osimertinib was similar to that among patients who received gefitinib or erlotinib, despite longer treatment exposure.[18,21] The efficacy and safety profile of osimertinib in patients with *EGFR* mutation–positive NSCLC advanced disease provide support for investigation of this agent as adjuvant treatment for resected disease.

The phase 3, randomized ADAURA trial assessed the efficacy and safety of osimertinib as compared with placebo in patients with completely resected stage IB to IIIA (as classified according to the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer [AJCC]),[22] *EGFR* mutation–positive (Ex19del or L858R) NSCLC, after adjuvant chemotherapy, according to physician and patient choice. After a planned review by the independent data monitoring committee in April 2020, the committee recommended that the trial be unblinded at a trial level 2 years early because of evidence of an efficacy benefit; we report the results of the unplanned interim analysis based on this recommendation.

Methods

Trial Patients

Full details of the trial have been published previously and are provided in the protocol and statistical analysis plan, available with the full text of this article at NEJM.org.[23] The trial design is shown in Figure S1 in the Supplementary Appendix (available at NEJM.org), and eligibility criteria are summarized in the Supplementary Methods section in the Supplementary Appendix. Eligible patients were at least 18 years of age (20 years of age or older in Japan and Taiwan), with a World Health Organization performance status of 0 or 1 (on a scale of 0 to 5, with higher numbers indicating greater disability); primary nonsquamous NSCLC with postsurgical pathological stage IB, II, or IIIA; and a centrally confirmed *EGFR* mutation (Ex19del or L858R, either alone or in combination with other *EGFR* mutations) on examination of tissue. At the time of recruitment, staging was determined according to the seventh edition of the *Cancer Staging Manual* of the AJCC. Complete resection of the primary NSCLC was mandatory. Administration of standard postoperative adjuvant chemotherapy before randomization was allowed but not mandatory; decisions about whether patients would receive adjuvant chemotherapy were made by the physician and the patient and were made before trial enrollment. Treatment with preoperative, postoperative, or planned radiation therapy was not allowed.

TRIAL OVERSIGHT

The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference for Harmonisation), applicable regulatory requirements, and the policy of the trial sponsor, AstraZeneca, on bioethics and human biologic samples. All the patients provided written informed consent.

The trial was funded by the sponsor and was designed by the investigators and the sponsor. The sponsor was responsible for collection and analysis of the data and had a role in data interpretation. The first draft of the manuscript was written by the first, second, and last authors, with medical-writing support funded by the sponsor and conducted in accordance with Good Publication Practice guidelines. All the authors had full access to the data, reviewed the manuscript before it was submitted for publication, and provided input. The authors vouch for the completeness and accuracy of the data and for the adherence of the trial to the protocol.

TRIAL DESIGN AND TREATMENT

In this phase 3, double-blind, placebo-controlled, randomized, international trial, patients were stratified according to disease stage (IB, II, or IIIA), *EGFR* mutational status (Ex19del or L858R), and race (Asian or non-Asian) and were randomly assigned in a 1:1 ratio to receive either oral osimertinib (at a dose of 80 mg once daily) or placebo. Screening and randomization occurred after the patients had undergone surgery and received chemotherapy. Patients received osimertinib or placebo for 3 years or until disease recurrence or fulfillment of a criterion for discontinuation.

TRIAL END POINTS

The primary end point was disease-free survival according to investigator assessment among patients with stage II to IIIA disease. The secondary end points included disease-free survival in the overall population of patients with stage IB to IIIA disease, overall survival, health-related quality of life, and safety. The analysis of quality-of-life data is ongoing, so those results are not reported here. Assessment of the site or sites of recurrence (including the CNS) and the time to CNS disease recurrence or death were prespecified exploratory end points.

TRIAL ASSESSMENTS

Disease-free survival was defined as the time from randomization to disease recurrence (determined by computed tomography or magnetic resonance imaging, pathological disease on biopsy, or both) or death from any cause. Baseline assessments were performed within 28 days before administration of osimertinib or placebo, with follow-up assessments at weeks 12 and 24, then every 24 weeks until 5 years, and yearly thereafter. At disease recurrence, sites of relapse were recorded. The assessment of safety and secondary end points is detailed in the Supplementary Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

The full analysis set, which included all the patients who underwent randomization, was used for demographic summaries and efficacy analyses. Safety data were summarized for the patients who received at least one dose of osimertinib or placebo.

Disease-free survival was analyzed with the use of a log-rank test stratified according to disease stage, mutational status, and race. The Breslow approach was used to handle tied events.

For the planned primary analysis, we determined that approximately 247 disease recurrence events or deaths in 490 patients with stage II to IIIA disease (50%) would provide 80% power to detect a hazard ratio of 0.70 at a two-sided alpha level of 5%. To control type I error at the 5% two-sided level, a prespecified hierarchical testing procedure was used; if significance was shown for disease-free survival among patients with stage II to IIIA disease, then disease-free survival would be tested for the overall population (patients with stage IB to IIIA disease). If this result was significant, overall survival would then be tested. The trial was not powered for overall survival.

The independent data monitoring committee met regularly to review safety. After a planned meeting in 2019 to assess futility, but not superiority, when at least 83 disease recurrence events or deaths had occurred in patients with stage II to IIIA disease, the committee requested assessment of efficacy data at the next scheduled meeting for safety (April 2020). On the basis of review of these data, the committee recommended that the trial be unblinded at a trial level early to complete primary reporting. Given these un-

planned reviews of efficacy for superiority, the alpha allocation had to be revised to control the overall type I error. Reviews of disease-free survival among patients with stage II to IIIA disease were conducted when 85 events and 156 events had been observed.

The planned data cutoff date for the primary event-based analysis was February 2022. The data cutoff date for this unplanned interim analysis was January 17, 2020.

RESULTS

PATIENTS AND TREATMENT

From November 2015 to February 2019, a total of 682 patients underwent randomization (339 to receive osimertinib and 343 to receive placebo) (Fig. S2). At the time of unblinding, enrollment was complete, and all the patients had been followed for at least 1 year. Baseline characteristics were balanced between the two groups (Table 1 and Table S1). Most patients with stage II to IIIA disease (76%) and approximately a quarter of the patients with stage IB disease (26%) received adjuvant platinum-based chemotherapy (Table S2).

In the overall population of patients with stage IB to IIIA disease, the median duration of total treatment exposure was 22.5 months (range, 0 to 38) in the osimertinib group and 18.7 months (range, 0 to 36) in the placebo group. The number of patients who discontinued osimertinib or placebo was 92 (27%) and 174 (51%), respectively. In the safety analysis, dose reductions were reported in 49 of 337 patients (15%) in the osimertinib group and in 3 of 343 patients (1%) in the placebo group. At the data cutoff date, 205 of 337 patients (61%) in the osimertinib group and 136 of 343 patients (40%) in the placebo group were continuing the assigned trial regimen.

EFFICACY

Among the 470 patients with stage II to IIIA disease, disease recurrence or death occurred in 156 patients (33% maturity); there were 26 events in the osimertinib group (11% maturity) and 130 events in the placebo group (55% maturity). The median follow-up for disease-free survival was 22.1 months in the osimertinib group and 14.9 months in the placebo group. The percentage of patients who were alive and disease-free at 24 months was 90% (95% confidence interval [CI], 84 to 93) in the osimertinib group and 44% (95% CI, 37 to 51) in the placebo group (overall hazard ratio for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26; P<0.001) (Fig. 1A). This hazard ratio, which was equal to an 83% reduction in the risk of disease recurrence or death, indicated a significantly longer disease-free survival among patients in the osimertinib group than among those in the placebo group. The median disease-free survival was not reached (95% CI, 38.8 to could not be calculated) in the osimertinib group and was 19.6 months (95% CI, 16.6 to 24.5) in the placebo group; Kaplan–Meier event curves showed early separation between the osimertinib and placebo groups.

In the overall population (682 patients), 196 patients (37 of 339 patients [11%] in the osimertinib group and 159 of 343 patients [46%] in the placebo group) had disease recurrence or died (29% maturity). The percentage of patients who were alive and disease-free at 24 months was 89% (95% CI, 85 to 92) in the osimertinib group and 52% (95% CI, 46 to 58) in the placebo group (overall hazard ratio for disease recurrence or death, 0.20; 99.12% CI, 0.14 to 0.30; P<0.001) (Fig. 1B). This hazard ratio, which equaled an 80% reduction in the risk of disease recurrence or death, indicated that disease-free survival was significantly longer among patients in the osimertinib group than among those in the placebo group. The median disease-free survival was not reached (95% CI, could not be calculated to could not be calculated) in the osimertinib group and 27.5 months (95% CI, 22.0 to 35.0) in the placebo group. A total of 24 of 37 patients (65%) in the osimertinib group and 149 of 159 patients (94%) in the placebo group were receiving osimertinib or placebo at disease recurrence; the remaining patients had discontinued the regimen before recurrence or had died.

The benefit favoring osimertinib with respect to disease-free survival was observed consistently across all predefined subgroups (Fig. 2), including disease stages IB, II, and IIIA (Fig. S3) and use or nonuse of adjuvant chemotherapy (Fig. S4). Among the patients with stage IB disease, the percentages of those who were alive and disease-free at 24 months were 88% (95% CI, 78 to 94) in the osimertinib group and 71% (95% CI, 60 to 80) in the placebo group (overall hazard ratio for disease recurrence or death, 0.39; 95% CI, 0.18 to 0.76); among those with stage II

disease, these percentages were 91% (95% CI, 82 to 95) and 56% (95% CI, 45 to 65), respectively (overall hazard ratio, 0.17; 95% CI, 0.08 to 0.31); and among those with stage IIIA disease, these percentages were 88% (95% CI, 79 to 94) and 32% (95% CI, 23 to 41), respectively (overall hazard ratio, 0.12; 95% CI, 0.07 to 0.20). Among the patients who received adjuvant chemotherapy, 89% (95% CI, 83 to 93) in the osimertinib group and 49% (95% CI, 41 to 56) in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.16; 95% CI, 0.10 to 0.26). Among the patients who did not receive adjuvant chemotherapy, 89% (95% CI, 81 to 94) in the osimertinib group and 58% (95% CI, 49 to 67) in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.23; 95% CI, 0.13 to 0.40).

In the overall population, locoregional-only recurrence was observed in 23 of 339 patients (7%) in the osimertinib group and in 61 of 343 patients (18%) in the placebo group (Table S3); 14 of 339 patients (4%) and 96 of 343 patients (28%), respectively, had distant recurrence (either distant only or with locoregional recurrence). Two deaths without disease recurrence occurred in the placebo group.

Recurrence of CNS-related disease or death occurred in 45 patients (6 of 339 patients [2%] in the osimertinib group and 39 of 343 patients [11%] in the placebo group); 4 patients (1%) and 33 patients (10%), respectively, had recurrence in the CNS. At 24 months, 98% of the patients (95% CI, 95 to 99) in the osimertinib group and 85% of the patients (95% CI, 80 to 89) in the placebo group were alive without CNS-related disease (overall hazard ratio for CNS disease recurrence or death, 0.18; 95% CI, 0.10 to 0.33). This hazard ratio indicated an 82% reduction in the risk of CNS disease recurrence or death with osimertinib. The median CNS disease-free survival was not reached (95% CI, 39.0 to could not be calculated) in the osimertinib group and was 48.2 months (95% CI, could not be calculated to could not be calculated) in the placebo group (Fig. 3).

At the data cutoff date, 29 patients in the overall population had died (9 in the osimertinib group and 20 in the placebo group) (see the Supplementary Results section and Fig. S5 in the Supplementary Appendix).

SAFETY

Overall, 680 patients were included in the safety analysis set (337 in the osimertinib group and 343 in the placebo group). Adverse events were reported in 329 patients (98%) in the osimertinib group and in 306 patients (89%) in the placebo group. Commonly reported adverse events (irrespective of causality) are listed in Table 2. Interstitial lung disease (grouped terms) was reported in 10 patients in the osimertinib group (3%) and in none of the patients in the placebo group. Adverse events that were considered by the investigator to be causally related to osimertinib or placebo are presented in Table S4. Adverse events of grade 3 or higher were reported in 68 patients (20%) in the osimertinib group and in 46 patients (13%) in the placebo group (Table S5). Serious adverse events were reported in 54 patients (16%) in the osimertinib group and in 42 patients (12%) in the placebo group (Table S6). No fatal adverse events were reported in the osimertinib group; one event (a pulmonary embolism) occurred in the placebo group. Dose interruptions, dose reductions, and discontinuation of the trial regimen owing to adverse events occurred in 80 (24%), 29 (9%), and 37 (11%) patients in the osimertinib group and in 37 (11%), 3 (1%), and 10 (3%) patients in the placebo group, respectively.

DISCUSSION

In the phase 3, double-blind, randomized international ADAURA trial, patients with resected *EGFR* mutation–positive NSCLC who received osimertinib had significantly longer disease-free survival than those who received placebo. With respect to the primary end point of disease-free survival, among patients with stage II to IIIA disease, 90% of those in the osimertinib group and 44% of those in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.17; 99.06% CI, 0.11 to 0.26; P<0.001). With respect to the key secondary end point of disease-free survival in the overall population of patients with stage IB to IIIA disease, 89% of those in the osimertinib group and 52% of those in the placebo group were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.20; 99.12% CI, 0.14 to 0.30; P<0.001), equating to an 80% reduction in the

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Osimertinib (N=339)	Placebo (N=343)
Sex — %		
Male	32	28
Female	68	72
Age — yr		
Median	64	62
Range	30–86	31–82
Smoking		
History — %		
Yes	32	25
No	68	75
Status — %		
Former	31	24
Never	68	75
Current	1	1
Pack-yr — mo		
Median	22	18
Range	0–360	0–130
Race — %†		
Asian	64	64
Non-Asian	36	36
WHO performance status — %‡		
0	64	64
1	36	36
AJCC stage — %§		
IB	32	32
II	34	34
IIIA	35	34
Histologic type — %		
Adenocarcinoma	96	97
Acinar adenocarcinoma	25	24
Malignant papillary adenocarcinoma	13	13
Malignant adenocarcinoma	54	55
Bronchioloalveolar adenocarcinoma	3	4
Solid adenocarcinoma with mucus formation	1	1
Non-adenocarcinoma	4	3
Bronchial gland carcinoma (not otherwise specified)	<1	1
Malignant adenosquamous carcinoma	1	1
Other	2	1

Table 1. (Continued.)

Characteristic	Osimertinib (N = 339)	Placebo (N = 343)
Lung cancer resection type — %		
Lobectomy	97	94
Other	<4	6
Sleeve resection	<1	1
Bilobectomy	2	2
Pneumonectomy	1	3
Regional lymph nodes — %		
N0	41	42
N1	29	28
N2	31	30
EGFR mutation type at randomization — (%)¶		
Ex19del	55	55
L858R	45	45
p.Thr790Met	1	1
Adjuvant chemotherapy — (%)		
Yes	60	60
No	40	40

* Percentages may not total 100 because of rounding. *EGFR* denotes epidermal growth factor receptor, Ex19del exon 19 deletion, L858R exon 21 codon p.Leu858Arg, and p.Thr790Met *EGFR* T790M resistance mutation.
† Race was reported by the investigators.
‡ A World Health Organization (WHO) performance status of 0 indicates that the patient is fully active and able to carry out all predisease activities without restrictions, and a WHO performance status of 1 indicates that the patient is restricted in physically strenuous activity but is ambulatory and able to carry out work of a light or sedentary nature, such as light housework or office work.
§ Staging was determined according to the seventh edition of the *Cancer Staging Manual* of the American Joint Committee on Cancer (AJCC).[22]
¶ *EGFR* mutational status at randomization was centrally tested. Patients may have had more than one *EGFR* mutation.

risk of disease recurrence or death with osimertinib. The disease-free survival benefit with osimertinib was observed consistently across all predefined subgroups, including all disease stages. Among the patients with stage IB disease, the percentages of those who were alive and disease-free at 24 months were 88% in the osimertinib group and 71% in the placebo group (overall hazard ratio for disease recurrence or death, 0.39); among those with stage II disease, these percentages were 91% and 56%, respectively (overall hazard ratio, 0.17); and among those with stage IIIA disease, these percentages were 88% and 32%, respectively (overall hazard ratio, 0.12).

The use of adjuvant chemotherapy according to disease stage before randomization in the ADAURA trial was consistent with the uptake reported in clinical trials and with practice in the community observed in real-world studies across different regions.[24-27] The majority of patients with stage II to IIIA disease and approximately a quarter of patients with stage IB disease received adjuvant chemotherapy; use was balanced across the two groups. The disease-free survival benefit with osimertinib was observed irrespective of whether patients received adjuvant chemotherapy or not. Of patients who received adjuvant chemotherapy, 89% who received osimertinib and 49% who received placebo were alive and disease-free at 24 months (overall hazard ratio for disease recurrence or death, 0.16); of patients who

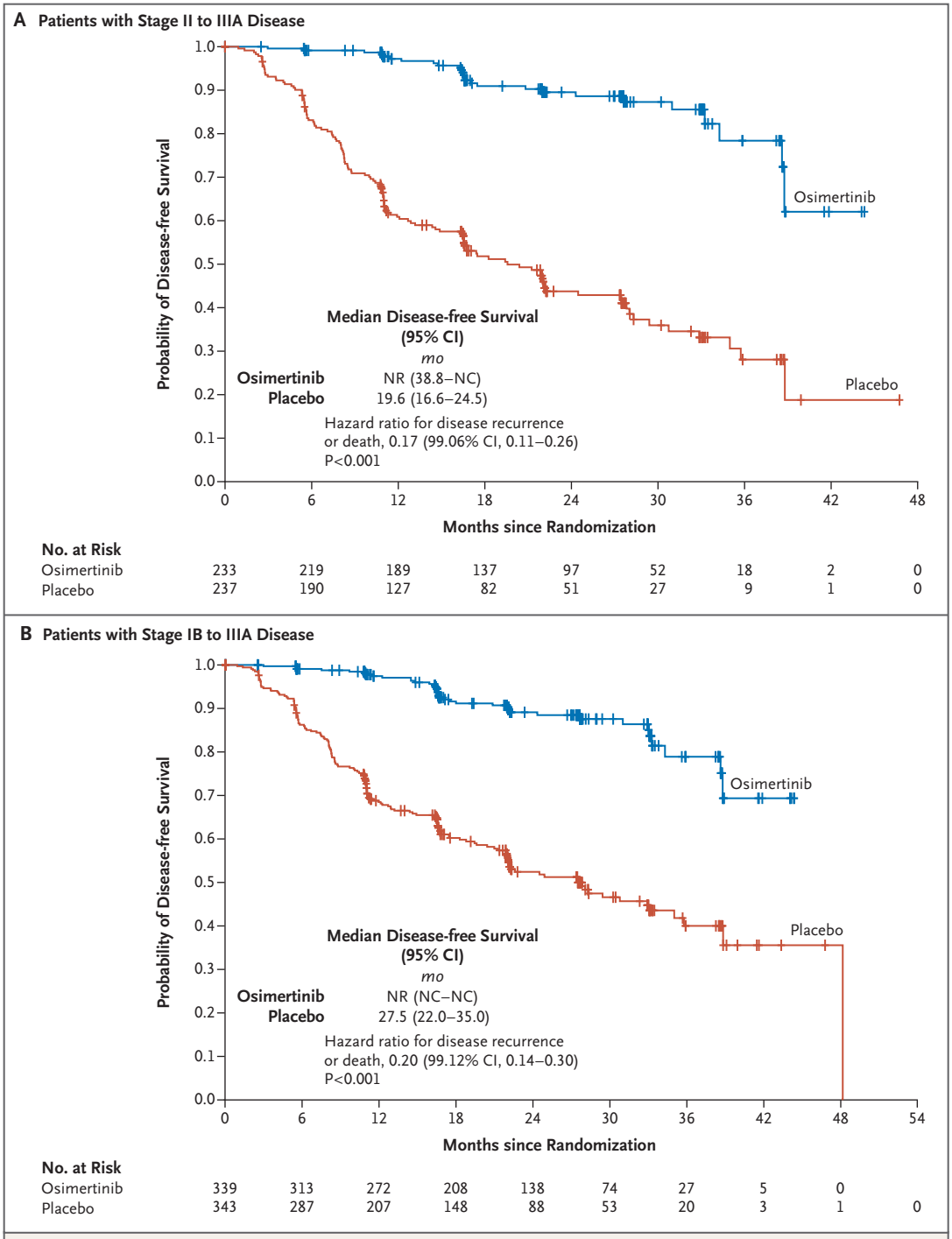

Figure 1. Disease-free Survival, According to Investigator Assessment.

Panel A shows Kaplan–Meier estimates of the duration of disease-free survival among patients with stage II to IIIA disease. At this interim analysis, a two-sided P value of less than 0.0094 was considered to be statistically significant. Panel B shows Kaplan–Meier estimates of the duration of disease-free survival in the overall population of patients with stage IB to IIIA disease. At this interim analysis, a two-sided P value of less than 0.0088 was considered to be statistically significant. Tick marks indicate censored data. CI denotes confidence interval, NC could not be calculated, and NR not reached.

did not receive adjuvant chemotherapy, these percentages were 89% and 58%, respectively (overall hazard ratio, 0.23).

The percentage of patients with disease recurrence was high in the placebo group, in line with similar historical data in unselected patients and *EGFR* mutation–positive patient populations; these results highlight the need for more effective adjuvant treatment options.[24,28-32] Patients who received osimertinib had fewer locoregional and distant relapses and fewer CNS recurrence events than those who received placebo (1% vs. 10%). The CNS is a common site of metastasis in NSCLC, and this metastasis indicates a poor prognosis.[33] In particular, *EGFR* mutations have been suggested to be a predictor of brain metastases in patients with stage I to III NSCLC.[34] In the ADAURA trial, a clinically meaningful increase in CNS disease-free survival was noted with osimertinib. At 24 months, 98% of the patients who received osimertinib and 85% of those who received placebo were alive without CNS disease (overall hazard ratio for CNS disease recurrence or death, 0.18; 95% CI, 0.10 to 0.33). Thus, adjuvant osimertinib reduced the risk of CNS recurrence among patients with resected *EGFR* mutation–positive NSCLC.

In patients with advanced NSCLC, EGFR-TKIs are well-established therapies, and *EGFR* mutation testing is the standard of care.[8-10] However, these advances have not been successfully applied in patients with resected NSCLCs. Results of the single-group SELECT trial suggested longer disease-free survival with adjuvant erlotinib among patients with *EGFR* mutation–positive stage IA to IIIA disease than among historical genotype-matched controls.[35] In the randomized, placebo-controlled RADIANT trial involving patients with stage IB to IIIA disease, adjuvant erlotinib was associated with longer disease-free survival in a post hoc analysis involving patients with *EGFR* mutation–positive disease, although this result was not significant and 37% of relapses in patients who received erlotinib involved

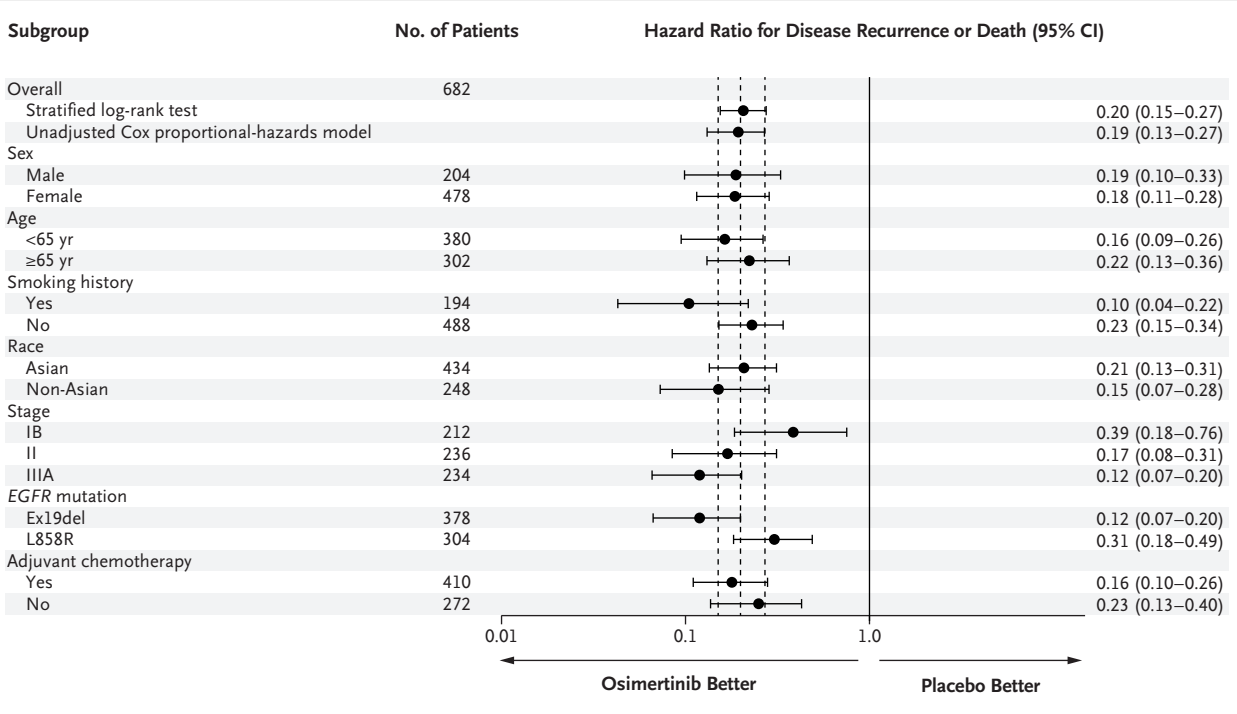

Figure 2. Subgroup Analysis of Disease Recurrence or Death, According to Investigator Assessment.

The subgroup analysis was performed with the use of a Cox proportional-hazards model that included trial regimen, subgroup, and the treatment-by-subgroup interaction term. Subgroup categories with less than 20 events were excluded from the analysis. Race was reported by the patients. The middle vertical dashed line indicates the median and the outer dashed lines indicate the 95% confidence interval for the overall hazard ratio (all patients). A hazard ratio of less than 1 implies a lower risk of disease recurrence or death with osimertinib than with placebo.

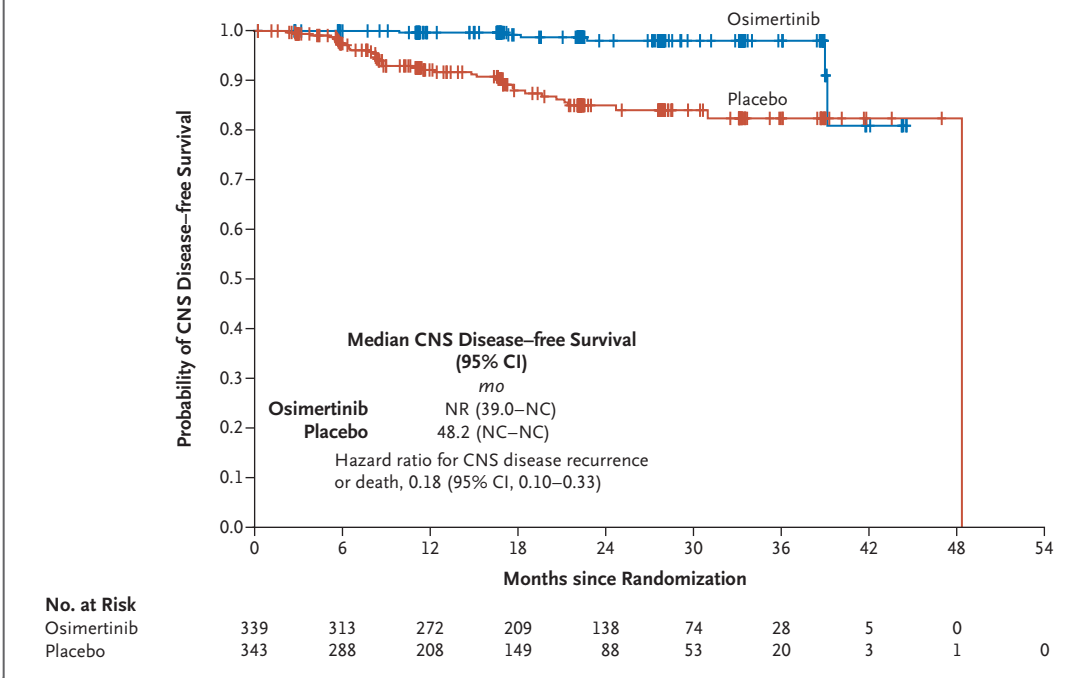

Figure 3. Central Nervous System (CNS) Disease–free Survival, According to Investigator Assessment in the Overall Population.

Shown is the Kaplan–Meier estimate of the duration of CNS disease–free survival in the overall population of patients with stage IB to IIIA disease. Tick marks indicate censored data.

the CNS.[24] The randomized EVAN trial showed longer disease-free survival at 2 years with adjuvant erlotinib than with chemotherapy among patients with *EGFR* mutation–positive stage IIIA disease.[31] The randomized ADJUVANT/CTONG1104 trial involving patients with *EGFR* mutation–positive stage II to IIIA disease showed longer disease-free survival among patients who received adjuvant gefitinib than among those who received chemotherapy (hazard ratio for disease recurrence or death, 0.60; 95% CI, 0.42 to 0.87; P=0.005).[30] However, the disease-free survival advantage did not translate to overall survival,[36] and recurrence in the CNS was common.[37] Although these results suggested a potential role of EGFR-TKIs in patients with resected *EGFR* mutation–positive NSCLC, they did not lead to changes in clinical practice.

The use of a highly potent and selective EGFR-TKI as adjuvant therapy in patients with tumors that may be less heterogeneous and more exclusively driven by *EGFR* mutations than tumors in those with advanced disease is hypothesized to lead to improved treatment outcomes.[16,38,39] Previous preclinical studies and clinical studies involving patients with advanced disease indicated that osimertinib could improve outcomes in patients with resected disease. Osimertinib has been shown to induce apoptosis and to have higher potency against mutant *EGFR* than gefitinib and erlotinib, with a profound and sustained effect in mutant *EGFR* tumor xenograft and transgenic models.[16,40] In addition, osimertinib has been shown to have more clinically significant exposure in the brain than other EGFR-TKIs.[41-43] In patients with advanced disease, first-line osimertinib has been shown to be superior to gefitinib or erlotinib with respect to progression-free and overall survival, with efficacy in CNS metastases, including a 52% reduction in the risk of CNS progression or death.[18,20,21] In our trial, the well-established efficacy of osimertinib that has been observed in patients with advanced disease was observed in patients with resected disease. Unlike previous trials of EGFR-TKIs, the efficacy results showed a substantial reduction in the risk of disease recurrence.

Overall survival results were immature at the

Table 2. Adverse Events.*

Adverse Event	Osimertinib (N=337)				Placebo (N=343)			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
	number of patients (percent)							
Diarrhea	156 (46)	116 (34)	32 (9)	8 (2)	68 (20)	54 (16)	13 (4)	1 (<1)
Paronychia	85 (25)	31 (9)	50 (15)	3 (1)	5 (1)	3 (1)	2 (1)	0
Dry skin	79 (23)	75 (22)	3 (1)	1 (<1)	22 (6)	18 (5)	4 (1)	0
Pruritus	65 (19)	49 (15)	16 (5)	0	30 (9)	28 (8)	2 (1)	0
Cough	62 (18)	43 (13)	19 (6)	0	57 (17)	42 (12)	15 (4)	0
Stomatitis	59 (18)	35 (10)	18 (5)	6 (2)	14 (4)	10 (3)	4 (1)	0
Nasopharyngitis	47 (14)	30 (9)	17 (5)	0	35 (10)	25 (7)	10 (3)	0
Upper respiratory tract infection	45 (13)	24 (7)	19 (6)	2 (1)	35 (10)	19 (6)	16 (5)	0
Decreased appetite	44 (13)	29 (9)	13 (4)	2 (1)	13 (4)	9 (3)	4 (1)	0
Mouth ulceration	39 (12)	32 (9)	7 (2)	0	8 (2)	6 (2)	2 (1)	0
Dermatitis acneiform	37 (11)	29 (9)	8 (2)	0	16 (5)	12 (3)	4 (1)	0

* Listed are adverse events that were reported in at least 10% of the patients in either trial group, according to the maximum Common Terminology Criteria for Adverse Events grade and preferred term. The safety analyses included all the patients who received at least one dose of osimertinib or placebo (safety analysis set). None of the adverse events reported in at least 10% of the patients in either trial group were determined to be grade 4 or higher.

time of this interim analysis. The patients and investigators have continued to remain unaware of the trial-group assignments, and follow-up is ongoing in order to report a more mature assessment of overall survival.

A low frequency of dose modifications and discontinuations of osimertinib and no new safety concerns were reported. All interstitial lung disease (grouped terms) events were mild or moderate in severity and were generally considered to be less clinically severe than those previously observed in patients with advanced disease, and all patients recovered. Furthermore, no notable differences between the trial groups were observed with respect to cardiac adverse events.

Future considerations for the ADAURA trial include subsequent treatment, longitudinal assessment of minimal residual disease, and acquired resistance mechanisms at relapse. The NeoADAURA (ClinicalTrials.gov number, NCT04351555) and LAURA (NCT03521154) trials are under way to investigate the efficacy and safety of neoadjuvant osimertinib in patients with *EGFR* mutation–positive resectable NSCLC and osimertinib after chemoradiation in stage III unresectable *EGFR* mutation–positive NSCLC, respectively.

In our international randomized trial, adjuvant osimertinib was associated with significant improvement in disease-free survival among patients with stage IB to IIIA *EGFR* mutation–positive NSCLC. Osimertinib as adjuvant therapy is an effective new treatment strategy for these patients after complete tumor resection.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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Health-Related Quality of Life Outcomes in Patients with Resected Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer Who Received Adjuvant Osimertinib in the Phase III ADAURA Trial

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ABSTRACT

Purpose: In the phase III ADAURA trial, adjuvant treatment with osimertinib versus placebo, with/without prior adjuvant chemotherapy, resulted in a statistically significant and clinically meaningful disease-free survival benefit in completely resected stage IB–IIIA EGFR-mutated (*EGFR*m) non–small cell lung cancer (NSCLC). We report health-related quality of life (HRQoL) outcomes from ADAURA.

Patients and Methods: Patients randomized 1:1 received oral osimertinib 80 mg or placebo for 3 years or until recurrence/discontinuation. HRQoL (secondary endpoint) was measured using the Short Form-36 (SF-36) health survey at baseline, 12, and 24 weeks, then every 24 weeks until recurrence or treatment completion/discontinuation. Exploratory analyses of SF-36 score changes from baseline until week 96 and time to deterioration (TTD) were performed in the overall population (stage IB–IIIA; $N = 682$). Clinically meaningful changes were defined using the SF-36 manual.

Results: Baseline physical/mental component summary (PCS/MCS) scores were comparable between osimertinib and placebo (range, 46–47) and maintained to Week 96, with no clinically meaningful differences between arms; difference in adjusted least squares (LS) mean [95% confidence intervals (CI), −1.18 (−2.02 to −0.34) and −1.34 (−2.40 to −0.28), for PCS and MCS, respectively. There were no differences between arms for TTD of PCS and MCS; HR, 1.17 (95% CI, 0.82–1.67) and HR, 0.98 (95% CI, 0.70–1.39), respectively.

Conclusions: HRQoL was maintained with adjuvant osimertinib in patients with stage IB–IIIA *EGFR*m NSCLC, who were disease-free after complete resection, with no clinically meaningful differences versus placebo, further supporting adjuvant osimertinib as a new treatment in this setting.

Introduction

For patients with NSCLC, approximately 30% will present with resectable disease, for which the primary treatment is surgery with curative intent (1–4). For patients with stage II–IIIA NSCLC, and select patients with stage IB disease, adjuvant cisplatin-based chemotherapy is recommended (4).

However, clinical outcomes remain poor across disease stages. A pooled analysis of data from patients with resected stage I–III NSCLC receiving adjuvant chemotherapy showed rates of disease

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Translational Relevance

In the phase III ADAURA trial, health-related quality of life (HRQoL), as assessed by the Short Form-36 (SF-36) health survey, was maintained during adjuvant osimertinib treatment, with or without prior adjuvant chemotherapy, in patients with completely resected stage IB–IIIA EGFR-mutated non–small cell lung cancer (NSCLC). No clinically meaningful differences with adjuvant osimertinib versus placebo were observed for the SF-36 component summaries or health domains. In addition to improving efficacy outcomes, a key goal of adjuvant treatment is to also maintain HRQoL as patients will be disease-free after surgery and may receive long-term treatment. Together with the previously reported significant disease-free survival (DFS) benefit with adjuvant osimertinib versus placebo and favorable safety profile of osimertinib, these HRQoL data provide further support for the use of adjuvant osimertinib as a new treatment strategy in this patient population.

recurrence following surgery ranging from 45% for stage IB to 76% for stage III disease, irrespective of postoperative chemotherapy use. The analysis also reported an overall HR for overall survival (OS) of 0.89 [95% confidence interval (CI), 0.82–0.96], corresponding to a 5-year absolute benefit of 5.4% with chemotherapy versus no chemotherapy, after a median follow-up time of 5.2 years (5).

In the advanced NSCLC setting, EGFR-tyrosine kinase inhibitors (EGFR-TKI) are standard of care in patients with *EGFR* mutations (refs. 6, 7; *EGFR*m). Osimertinib, a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits EGFR-TKI sensitizing and *EGFR* T790M resistance mutations with proven efficacy in central nervous system metastases (8–12), is now considered the preferred first-line option for patients with *EGFR*m advanced NSCLC (6, 7). Because of this benefit in the advanced setting, adjuvant osimertinib was assessed in patients with resectable stage IB–IIIA *EGFR*m NSCLC in the phase III ADAURA trial and demonstrated a highly statistically significant and clinically meaningful improvement in DFS versus placebo (HR, 0.20; 99.12% CI, 0.14–0.30; $P < 0.001$; ref. 13). The data also demonstrated a safety profile consistent with that known for osimertinib, with a low frequency of dose modifications and discontinuations and no new safety signals reported (13), with or without chemotherapy (14). Subsequently, osimertinib has been approved in the US, China, the EU, the UK, and multiple countries worldwide, for use as an adjuvant treatment in patients with resectable *EGFR*m (Ex19Del/L858R) NSCLC (15–18).

As established in other adjuvant cancer settings, the effect of adjuvant treatment on HRQoL is an important clinical consideration for patients who, following surgery with curative intent, are disease-free and require long-term treatment to reduce the risk of disease recurrence (4, 19–22). The goal of treatment in the adjuvant setting is therefore to improve efficacy outcomes while also maintaining HRQoL (19). However, in the adjuvant NSCLC setting, HRQoL data are limited, and comprise of two studies showing a transient, modest worsening or no impact on HRQoL with different chemotherapy regimens in patients with resected stage IB–III NSCLC (23, 24), and one study reporting significantly improved HRQoL with the EGFR-TKI gefitinib versus chemotherapy in patients with resected stage II–IIIA *EGFR*m NSCLC (25), although comparison between studies is limited because of the application of different QoL instruments and treatments evaluated.

Here, we report HRQoL outcomes from ADAURA, which is the first global, randomized, phase III trial in the adjuvant, resected *EGFR*m NSCLC setting to evaluate HRQoL with an EGFR-TKI versus placebo, with or without prior adjuvant chemotherapy (13, 26–28).

Patients and Methods

Patients, trial design, and treatment

Details of the ADAURA trial design (NCT02511106) have been previously published (13, 29). Briefly, the phase III double-blind, randomized, placebo-controlled, global ADAURA trial enrolled adult patients (≥18 years; ≥20 years in Japan and Taiwan) with histologically confirmed primary non-squamous NSCLC of post-surgical pathological stage IB, II, or IIIA [American Joint Committee on Cancer (AJCC) 7th edition; ref. 30], central confirmation of *EGFR* mutation [exon 19 deletions (Ex19Del) or exon 21 codon p.Leu858Arg (L858R) point mutations], and a World Health Organization performance status of 0 or 1. Complete surgical resection of the primary NSCLC (with negative margins) was required, and postoperative adjuvant chemotherapy before randomization was allowed, but not mandatory, per physician and patient choice. Patients were stratified according to disease stage (IB, II, or IIIA), *EGFR* mutational status (Ex19Del or L858R), and race (Asian or non-Asian), and randomized 1:1 to oral osimertinib 80 mg once daily or placebo following complete resection and adjuvant chemotherapy, if indicated. Treatment continued for 3 years or until disease recurrence or other discontinuation criteria were fulfilled.

The primary endpoint was investigator-assessed DFS in patients with stage II–IIIA disease and secondary endpoints included DFS in the overall population (stage IB–IIIA disease), OS, HRQoL, and safety. An interim analysis of the primary and key secondary endpoints has been reported previously (13). The data cutoff value (DCO) for the previously reported primary analysis and this HRQoL analysis was January 17, 2020.

The study was approved by the institutional review board or independent ethics committee associated with each study center. The trial was conducted in accordance with the provisions of the Declaration of Helsinki, Good Clinical Practice guidelines (as defined by the International Conference for Harmonization), applicable regulatory requirements, and policy of the trial sponsor, AstraZeneca, on bioethics and human biologic samples. All patients provided written informed consent.

HRQoL endpoints and data collection

HRQoL was assessed using the SF-36 health survey version 2 (31), which measures a patient's general health status with a recall period of 4 weeks. The SF-36 collects scores from 36 items across eight health domains [Physical Functioning (PF), Role Limitations–Physical (RP), Vitality (VT), General Health Perceptions (GH), Bodily Pain (BP), Social Function (SF), Role Limitations- Emotional (RE), and Mental Health (MH)] and produces two weighted aggregate scores, the physical component summary (PCS) and the mental component summary (MCS). All eight health domains contribute to the PCS and MCS, but the PF, RP, BP, and GH domains contribute most strongly to the PCS, and the VT, SF, RE, and MH domains contribute most strongly to the MCS. SF-36 data were collected at randomization (predose), weeks 12 and 24 after randomization, and then every 24 weeks until disease recurrence, treatment completion (at 3 years), or treatment discontinuation, whichever occurred first. At treatment discontinuation due to disease recurrence or other discontinuation criteria, HRQoL data were collected at the treatment discontinuation visit; however, no further HRQoL data were collected afterwards. To

minimize bias, SF-36 surveys were completed before any investigations or discussions with the clinical staff or physicians on the day of the patient visit, so patients would not have been aware of any changes in their disease status, such as disease progression, before completing the survey.

SF-36 scores were calculated as follows, using a norm-based scoring method. Briefly, 0–100 scores for each of the health domain scales and component summary measures (PCS and MCS) were transformed to T-scores using standard score formulas based on the 2009 US general population's mean values (normative mean): The mean T-score in the 2009 US population is 50, with an SD of 10 (31). Higher T–scores indicate better health (31). T-scores above and below 50 are above and below the average, respectively, of the 2009 US population. With the SD being 10, each 1-point change in T-scores is interpreted as one-tenth of an SD and has an effect size of 0.1 (31). Missing responses in the SF-36 health survey were imputed using the SF-36 Full Missing Score Estimation procedure, which uses a combination of the respondent's available health domain scale and component summary measure scores (31).

The Full Missing Score Estimation procedure was used for imputing missing responses in the SF-36 health survey (31). A given health domain score [except for physical functioning (PF)] can be estimated when the patient provides a response to at least one item in that scale and regression methods are used to estimate component summary measure scores based on the available scales (31). The model assumes that the missing item response(s) in one scale are the same as the response to the scale's single answered item, or the average of all responses, if more than one item has been answered (31). For the PF scale, which comprises items that vary greatly in difficulty across the scale, estimates of missing values were obtained using the item response theory (IRT) method. At least one item within the scale needs to be answered to be able to compute the scale's score. An IRT model generates values that indicate the probability of a respondent selecting a specific response to a given item, based on their responses to previously answered items in the PF scale (31).

The PCS and MCS scores were estimated for a patient who had data for at least seven of the eight health domain scales and was not missing the following required scale scores: PF for calculation of the PCS score and MH for calculation of the MCS score. If a patient had a fully completed MCS (with no domain scales missing from the calculation), then the PCS score was also calculated completely with no missing domains and vice versa, because all eight health domain scales contribute to the scoring of both MCS and PCS with different weighting. If the MCS score was calculated (and it was missing the PF domain only), then the PCS score was not calculated. Vice versa, if the PCS score was calculated (and it was missing the MH domain only), then the MCS score was not calculated. Among 682 randomized patients, only one patient had MCS score but missing PCS score (due to missing PF domain score) at the Week 156 visit.

Both pre-specified and exploratory analyses of HRQoL were conducted. The pre-specified, per-protocol HRQoL analyses included a time to deterioration (TTD) analysis of the SF-36 PCS and MCS in patients with stage II–IIIA disease, using values for clinically meaningful differences defined in the 2nd edition of the SF-36 scoring manual (32).

The exploratory, *post hoc* HRQoL analyses included a mixed model of repeated measures (MMRM) of change from baseline up to Week 96 in SF-36 PCS, MCS, and health domain scores, and a TTD analysis of the SF-36 PCS, MCS, and health domain scores. Both MMRM and TTD analyses were conducted in the overall population (stage IB–IIIA disease) using clinically meaningful differences assigned on the basis of the values defined in the most recent 3rd edition of the SF-36 scoring manual (31). Values of clinically meaningful differences for MMRM and TTD analyses defined in the 2nd and 3rd editions of the SF-scoring manual are reported in Supplementary Table S1. Changes from baseline were only calculated until Week 96 to ensure balanced comparison between the treatment arms, as earlier discontinuations in completing the SF-36 survey were observed in the placebo arm compared with the osimertinib arm due to earlier disease recurrence.

Statistical analysis

The SF-36 compliance over time was calculated for each visit, including baseline, as the number of patients with an evaluable questionnaire (a questionnaire with a completion date and at least one health domain that was non-missing) at that visit, divided by the number of patients still expected to complete the questionnaire.

The MMRM analysis was performed on the change from baseline in SF-36 PCS, MCS, and health domain scores at each visit up to Week 96, which was averaged across visits over 96 weeks for the osimertinib and placebo arms. The MMRM analysis included patient (as a random effect), treatment and visit (as a fixed effect and repeated measure), and treatment-by-visit interaction as explanatory variables, as well as baseline score and baseline score-by-visit interaction as covariates, using an unstructured covariance structure.

TTD was defined as the time from randomization to the first clinically important worsening, confirmed at the subsequent assessment, or death by any cause in the absence of a clinically important worsening, providing that death occurred within two assessment visits from the last HRQoL assessment, and regardless of whether the patient withdrew from study treatment or received another anticancer therapy before symptom deterioration. TTD was analyzed using a log-rank test stratified by stage (II vs. IIIA, for analyses conducted in patients with stage II–IIIA disease; IB vs. II vs. IIIA, for analyses conducted in the overall population), *EGFR* mutation type (Ex19Del vs. L858R), and race (Asian vs. non-Asian). Summary statistics for TTD of SF-36 PCS, MCS, and health domain scores were calculated using the Kaplan–Meier method. The HR and CI were obtained directly from the U and V statistics, as previously described (13, 33, 34). Patients with two missed visits before confirmed deterioration were censored at the last evaluable assessment before the two missed visits.

Data availability statement

Data underlying the findings described previously in this article may be obtained in accordance with AstraZeneca's data sharing policy described previously at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

Results

Patients and treatment

A total of 682 patients with stage IB–IIIA *EGFR*m NSCLC were randomized with 339 receiving osimertinib and 343 receiving placebo (13). Baseline demographics and clinical characteristics for these patients have been previously published by Wu and colleagues (13) and were balanced between treatment arms. At DCO (January 17, 2020) in the osimertinib and placebo arms, respectively, the median (range) duration of treatment exposure was 22.5 (0–38) months and 18.7 (0–36) months, and 12% and 10% of patients had completed the 3-year study treatment (13).

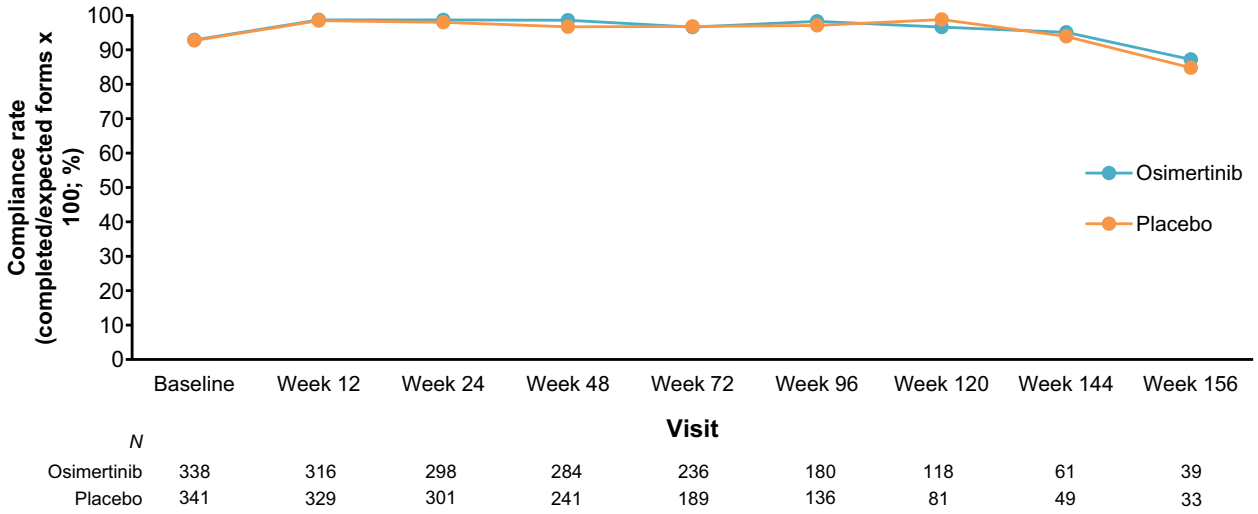

Figure 1.

Compliance rates with the SF-36 survey in the overall population. Compliance rates were calculated as the number of evaluable forms (*n*) divided by the number of expected forms (*N*), multiplied by 100, at 12- or 24-week intervals from baseline to week 156. The expected number of SF-36 forms is shown under each timepoint. SF-36, Short Form-36 health survey.

SF-36 compliance

Compliance with the SF-36 survey ranged from 85% to 99% for the overall population from baseline through to Week 156 (**Fig. 1**). During this period, SF-36 compliance rates were similar with osimertinib (87%–99%) and placebo (85%–99%; **Fig. 1**).

Baseline SF-36 scores

In the overall population, baseline mean (SD) SF-36 PCS and MCS T-scores were comparable between the osimertinib and placebo arms: PCS, 47.09 (7.4) and 46.61 (7.4); MCS, 46.37 (10.4), and 46.82 (10.8), respectively (**Fig. 2**). These T-scores were slightly lower (0.3–0.4 SD below the normative mean) than those in the general population. Individual SF-36 health domain T-scores were also similar between the two treatment arms with the majority being within ±0.3 SD of the normative mean and therefore comparable with the general population. However, greater impairment was observed for the role-physical, social functioning, and role-emotional domains with T-scores 0.5–0.8 SD below the normative mean (**Fig. 2**).

Change in SF-36 scores (MMRM analyses)

In patients receiving osimertinib in the overall population, SF-36 PCS and MCS were maintained from baseline up to Week 96, with no clinically meaningful differences observed compared with the placebo arm (**Fig. 3**). In the osimertinib and placebo arms, from baseline to Week 96, the adjusted least squares (LS) mean for PCS score numerically increased by 1.13 (95% CI, 0.54–1.72) and 2.31 (95% CI, 1.70–2.91), respectively, and the adjusted LS mean for MCS score numerically increased by 1.34 (95% CI, 0.60–2.08) and 2.68 (95% CI, 1.92–3.44), respectively (**Table 1**). The resulting treatment difference for the adjusted LS mean change was −1.18 (95% CI, −2.02 to −0.34) for the

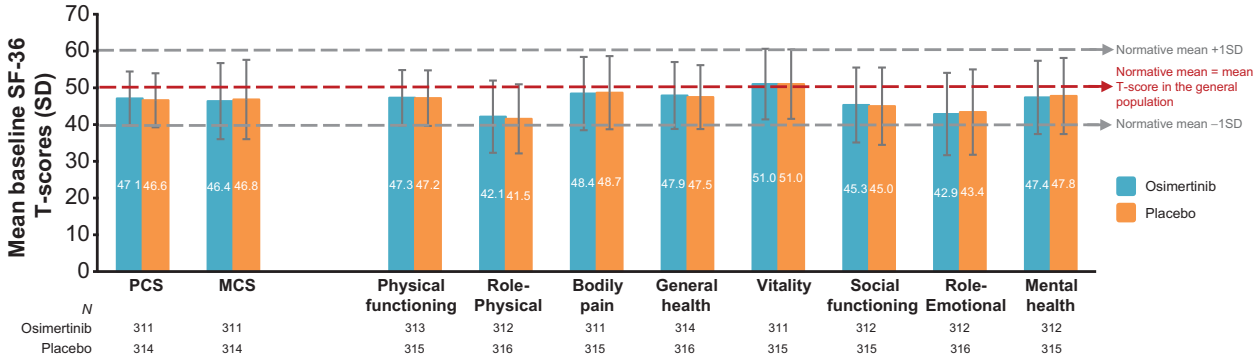

Figure 2.

Baseline T-scores of the SF-36 component summaries and health domains in the overall population. The red dashed line shows the mean 2009 U.S. population SF-36 normative mean calculated from a sample of adults aged ≥18 years, including healthy individuals, and those with chronic conditions (31); normative data are not age-adjusted. The gray dashed lines show this normative mean ± 1SD. The number of patients with data available at each visit is shown below each component summary and health domain. MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36 health survey.

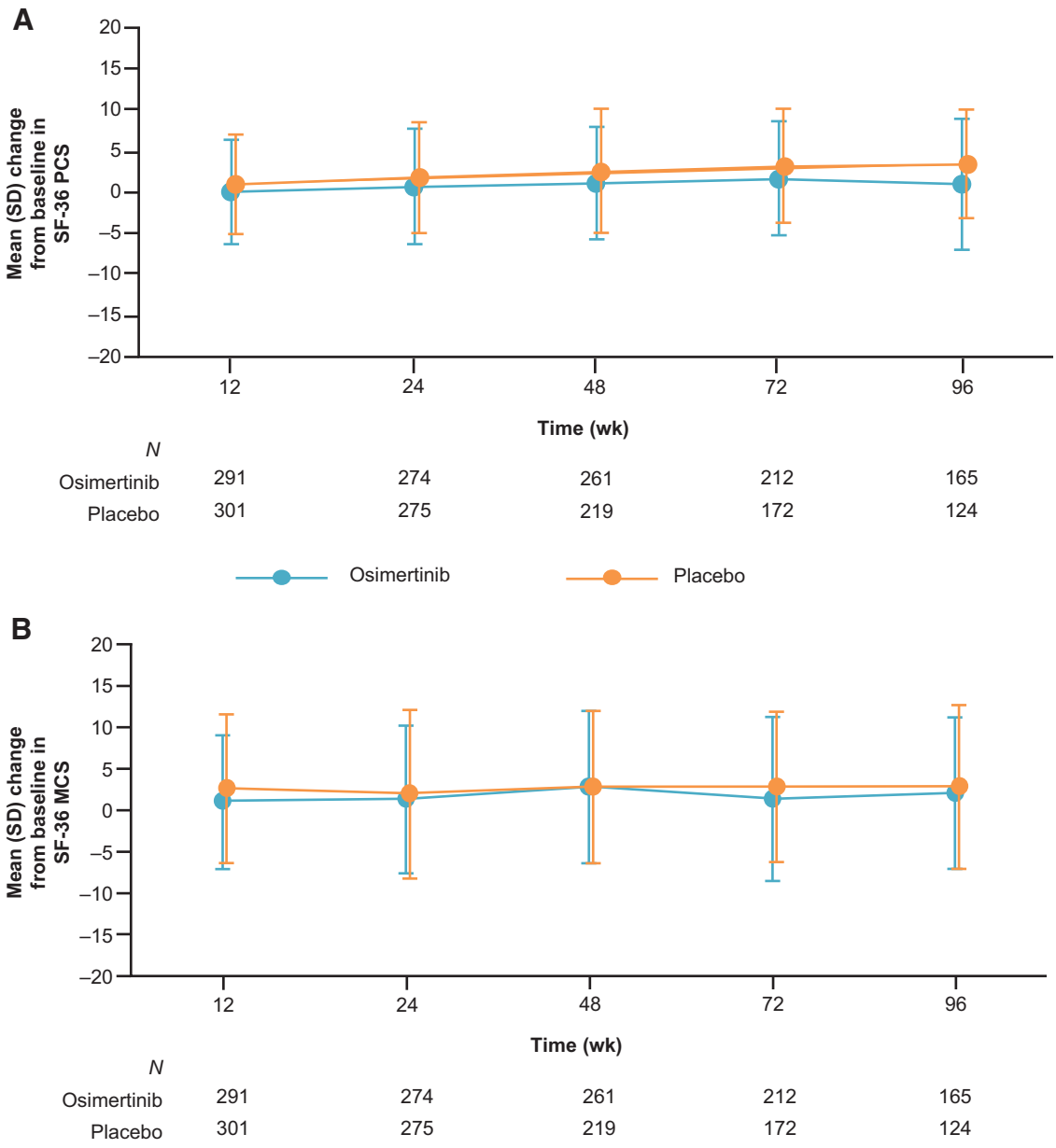

Figure 3.

Change in SF-36 (**A**) PCS and (**B**) MCS T-scores from baseline to week 96 in the overall population. The data shown are mean change from baseline in T-scores with error bars representing the SDs. The number of patients with data available at each visit is shown below each timepoint. MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36 health survey.

PCS score and −1.34 (95% CI, −2.40 to −0.28) for the MSC score, neither of which represented a clinically meaningful difference between treatment arms, according to the definitions from the 3rd edition of the SF-36 scoring manual (**Table 1**; ref. 31). Similarly, SF-36 health domains T-scores were maintained from baseline to Week 96 with osimertinib treatment, with numerical increases across the majority of domains in both arms (**Table 1**). On the basis of the 3rd edition of the SF-36 scoring manual definitions (31), no clinically meaningful differences were observed for any health domain with osimertinib compared with placebo (**Table 1**).

TTD in SF-36 score analyses

In the overall population during the treatment period, 81% and 84% of patients in the osimertinib and placebo arms, respectively, did not experience a clinically meaningful deterioration in the PCS or death, and 81% in both treatment arms did not experience a clinically meaningful deterioration in the MCS or death; definitions for clinically meaningful differences were based on the 3rd edition of the SF-36 scoring manual (31). In patients who did experience deterioration, there were no differences in TTD of the PCS (HR, 1.17; 95% CI, 0.82–1.67) or MCS (HR, 0.98; 95% CI, 0.70–1.39) between the osimertinib

Table 1. MMRM adjusted LS mean change from baseline up to week 96 in SF-36 component summaries and health domain T-scores in the overall population.

SF-36 component summary or health domain	MMRM adjusted LS mean change from baseline (95% CI)			Clinically meaningful difference[a]
	Osimertinib	Placebo	Osimertinib–placebo	
PCS	1.13 (0.54–1.72) *n* = 293	2.31 (1.70–2.91) *n* = 303	−1.18 (−2.02 to −0.34)	±2
MCS	1.34 (0.60–2.08) *n* = 293	2.68 (1.92–3.44) *n* = 303	−1.34 (−2.40 to −0.28)	±3
Physical functioning	0.53 (−0.10 to 1.16) *n* = 295	1.38 (0.74–2.03) *n* = 303	−0.86 (−1.76 to 0.04)	±3
Role-physical	2.67 (1.91–3.43) *n* = 294	4.47 (3.69–5.25) *n* = 304	−1.80 (−2.90 to −0.71)	±3
Bodily pain	1.66 (0.91–2.40) *n* = 293	2.22 (1.45–2.99) *n* = 303	−0.57 (−1.64 to 0.50)	±3
General health	−0.41 (−1.12 to 0.31) *n* = 296	1.09 (0.36–1.83) *n* = 304	−1.50 (−2.53 to −0.47)	±2
Vitality	0.98 (0.22–1.74) *n* = 293	2.91 (2.13–3.69) *n* = 304	−1.93 (−3.02 to −0.84)	±2
Social functioning	2.77 (2.06–3.49) *n* = 294	3.88 (3.14–4.62) *n* = 303	−1.11 (−2.13 to −0.08)	±3
Role-emotional	1.05 (0.22–1.87) *n* = 294	2.51 (1.66–3.36) *n* = 304	−1.46 (−2.65 to −0.28)	±4
Mental health	1.17 (0.44–1.90) *n* = 294	2.05 (1.30–2.80) *n* = 304	−0.88 (−1.92 to 0.17)	±3

Abbreviations: CI, confidence interval; LS, least squares; MCS, mental component summary; MMRM, mixed model of repeated measures; PCS, physical component summary; SF-36, Short Form-36 health survey.
[a]Clinically meaningful difference based on definitions from the 3rd edition of the SF-36 scoring manual (31).

and placebo arms (**Fig. 4**). There were also no differences between the osimertinib and placebo arms in the TTD for all SF-36 health domains with HRs ranging from 0.68 to 1.19 (**Fig. 5**).

Comparable results were obtained when using clinically meaningful differences as defined by the 2nd edition of the SF-36 scoring manual (31) in the overall patient population and in the pre-specified analysis in patients with stage II–IIIA disease; the pre-specified analysis is presented in Supplementary Figs. S1 and S2. In the overall patient population, the HRs for TTD of the PCS and MCS were 1.25 (95% CI, 0.90–1.73) and 0.95 (95% CI, 0.69–1.30), respectively (Supplementary Fig. S3), and the HRs for TTD of the eight health domains ranged from 0.93 to 1.19 (Supplementary Fig. S4).

Discussion

Previous results from the primary analysis of the ADAURA trial showed a statistically significant improvement in DFS with adjuvant osimertinib versus placebo in patients with completely resected stage IB–IIIA *EGFR*m NSCLC (13). At the time of this analysis, the OS data were immature and the follow-up for OS continues. The ADAURA analysis reported here assessed the effect of adjuvant osimertinib versus placebo on HRQoL in patients who were disease-free following surgery, with or without prior adjuvant chemotherapy. Overall, the data demonstrated that HRQoL was maintained with adjuvant osimertinib treatment, with no clinically meaningful differences versus placebo in the SF-36 component summaries and individual health domain scores.

HRQoL was measured in ADAURA using the SF-36 health survey, which is a widely used and validated international non–cancer-specific questionnaire that comprehensively measures patients' general functional status and well-being, regardless of age, disease, or treatment received (31). At the time of designing the ADAURA trial, the SF-36 had been translated into 10 languages, making it an accessible tool, and has been used in other adjuvant cancer settings, such as breast and gastric cancers (21, 22, 35–37). A generic survey, rather than a cancer-specific one, was chosen as patients were considered cancer-free before receiving osimertinib/placebo, as per the trial inclusion criteria. Furthermore, SF-36 assessments were performed only until disease recurrence, a period during which patients were considered not to have physical symptoms of cancer, although were recovering from surgery and could potentially suffer from emotional and psychological effects of, for example, chemotherapy or their recent lung cancer diagnosis, which could affect their general HRQoL. SF-36 provides a comprehensive measure of global HRQoL and comprises 36 items assessing patients' general health on 8 multi-item dimensions (38). As such, it is a sensitive tool for measuring general HRQoL: It can capture the impact of any general health event on HRQoL, and provide useful insights into the effects of adjuvant osimertinib treatment on overall HRQoL, including social and emotional functioning, in patients who are disease-free.

HRQoL was a pre-specified endpoint in ADAURA. Pre-specified, per-protocol analyses included a TTD analysis of PCS and MCS in patients with stage II–IIIA disease (primary analysis population; ref. 13) using values for clinically meaningful differences defined in the 2nd edition of the SF-36 scoring manual (32). The main HRQoL results presented here were exploratory, *post hoc* analyses, as they were based on the most recent (3rd) edition of the SF-36 scoring manual (31) and used data from the overall population (stage IB–IIIA disease), which includes more patients than the primary analysis population (stage II–IIIA disease) used in the prespecified analysis. The use of the overall population in these exploratory HRQoL analyses was deemed reasonable as the results from the primary endpoint, DFS, in patients

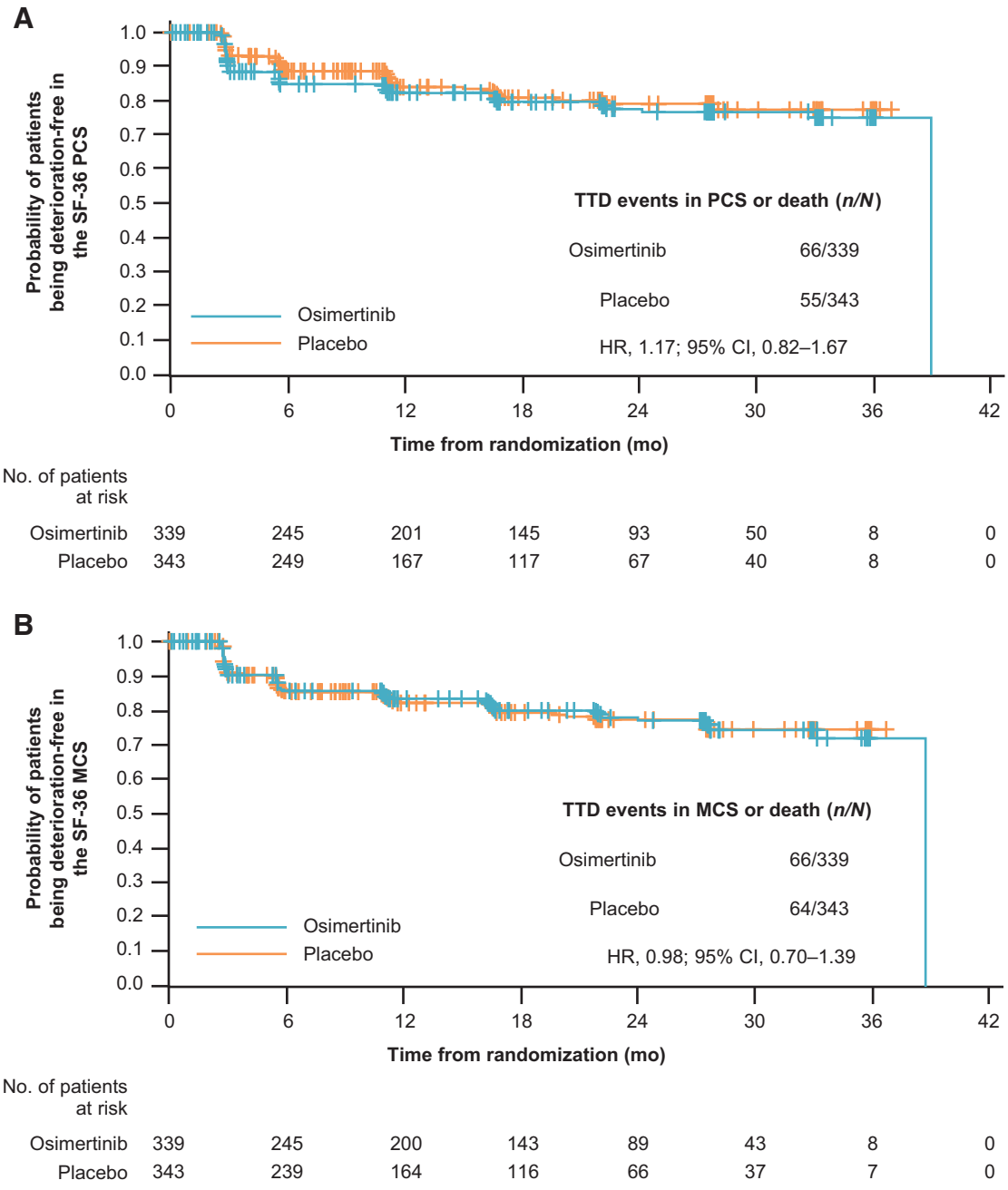

Figure 4.

TTD of the SF-36 (**A**) PCS and (**B**) MCS in the overall population. Kaplan–Meier plots are shown for the TTD analysis using clinically meaningful differences defined in the 3rd edition of the SF-36 scoring manual (31). The number of TTD events in MCS/PCS or death (*n*) in the overall population (*N*) are shown along with the HRs and 95% CIs comparing the treatment arms. The analysis was performed using an unstratified log-rank test due to low event counts. Crosses indicate censored patients, and the number of patients at risk is shown below each timepoint. CI, confidence interval; MCS, mental component summary; PCS, physical component summary; SF-36, Short Form-36 health survey; TTD, time to deterioration.

with stage II–IIIA disease (HR, 0.17; 99.06% CI, 0.11–0.26; $P < 0.001$), were similar to those reported for the overall population (HR, 0.20; 99.12% CI, 0.14–0.30; $P < 0.001$; ref. 13). Indeed the results from the TTD analyses of SF-36 PCS and MCS were similar when using the definition of clinically meaningful difference from either the 2nd or 3rd edition of the SF-36 scoring manual (31, 32) and the overall conclusions from these HRQoL analyses remained the same irrespective of the SF-36 manual edition used.

It should be noted that no HRQoL data were collected after treatment discontinuation, due to disease recurrence or other discontinuation criteria, as the objective of these analyses was to assess patients' HRQoL while they were receiving randomized treatment.

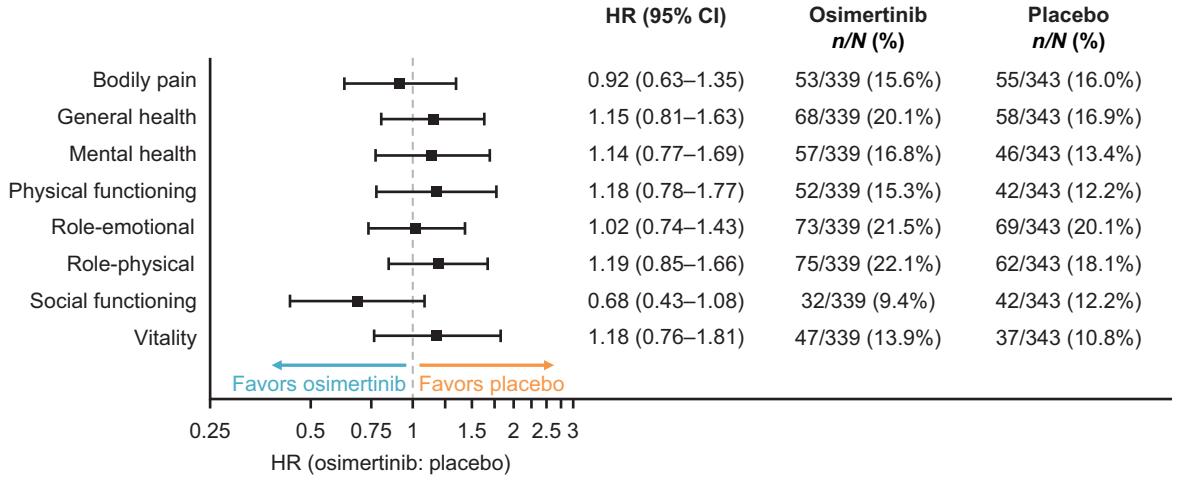

Figure 5.

Forest plot of the TTD of the SF-36 health domains in the overall population. The TTD analysis used clinically meaningful differences defined in the 3rd edition of the SF-36 scoring manual (31) and was performed using an unstratified log-rank test due to low event counts. HRs and corresponding 95% CIs are shown for each health domain along with the number of events (*n*) in the overall population (*N*). An HR <1 favors osimertinib treatment. CI, confidence interval; SF-36, Short Form-36 health survey; TTD, time to deterioration.

In addition, interpretation of post-recurrence HRQoL data may have been confounded by subsequent treatments, so it would have been difficult to isolate the effect of adjuvant osimertinib on HRQoL after disease recurrence. However, as recurrence rates were higher in the placebo arm versus the osimertinib arm in ADAURA, and with HRQoL outcomes predicted to decrease upon disease recurrence (36), the overall between-arm difference in HRQoL would likely be favoring osimertinib. This will not be explored further in the ongoing ADAURA trial, but analysis of long-term HRQoL data following disease recurrence will be important in future studies.

In patients who were disease-free following surgery, with or without prior adjuvant chemotherapy, baseline SF-36 PCS and MCS T-scores were comparable in the osimertinib and placebo arms, and only slightly lower than the mean T-scores in the general population. The majority of health domain scores were comparable with the general population; exceptions to this were for role-physical, social functioning, and role-emotional, which were lower than the general population. This may have been due to the impact of surgery, chemotherapy, or the patients' recent lung cancer diagnosis on these aspects of QoL, although patients were randomized once they had sufficiently recovered from surgery and completed adjuvant chemotherapy. Overall, the data indicated that patients enrolled in ADAURA were highly functioning in terms of HRQoL.

Both the MMRM and TTD analyses presented here were chosen to provide a comprehensive assessment of HRQoL with adjuvant osimertinib. Although the TTD analysis as presented here is an accepted method for assessing HRQoL in cancer studies (39–41), including NSCLC studies, it does not capture what happens to the patient after they experience deterioration in HRQoL. The MMRM analysis is, therefore, complementary to the TTD as it evaluates HRQoL scores in a continuous manner across visits and assesses change from baseline (39, 40). In the MMRM analysis, the SF-36 PCS, MCS, and individual health domains were maintained from baseline up to Week 96 during osimertinib treatment in patients who were disease-free following complete resection, with no clinically meaningful differences observed compared with placebo. More than 80% of patients across both arms did not experience a clinically meaningful deterioration in the SF-36 PCS and MCS and, for those patients who had deterioration, there were no differences in TTD for these summaries and the individual health domains between osimertinib and placebo.

Only a few other studies have reported the effect of adjuvant chemotherapy or EGFR-TKIs on HRQoL in patients with resected stage IB–IIIA NSCLC and have used cancer-specific questionnaires to assess HRQoL (23–25). In the JBR.10 study, adjuvant cisplatin and vinorelbine was associated with a modest and temporary worsening of the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) in patients with resected stage IB–II NSCLC, with return to baseline function by 9 months in most patients (23). Other chemotherapy regimens, such as gemcitabine plus cisplatin and docetaxel plus cisplatin, do not appear to have any significant negative impact on EORTC QLQ-C30 in patients with stage IB–III NSCLC (24). In the ADJUVANT/CTONG 1104 study, the EGFR-TKI gefitinib compared with cisplatin plus vinorelbine showed significantly improved scores across three HRQoL instruments (functional assessment of cancer therapy-lung cancer, lung cancer symptom scale, and trial outcome index) and was associated with longer TTD in these HRQoL scores in Chinese patients with resected stage II–IIIA *EGFR*m NSCLC (25). Several phase III trials of adjuvant immunotherapy, with or without adjuvant chemotherapy, versus placebo/observation/best supportive care are currently ongoing in the resected stage IB–IIIA NSCLC setting (42–45); however, HRQoL data are only anticipated from one randomized phase III trial of adjuvant durvalumab (NCT02273375; ref. 45).

Several limitations should be considered when analyzing these results. First, the data presented are from exploratory analyses (stage IB–IIIA disease, 3rd edition of the SF-36 scoring manual); however, the results of these analyses are in line with the pre-specified analyses (stage II–IIIA disease, 2nd edition of the SF-36 scoring manual). Because of the earlier than planned DCO, the proportion of patients who completed the 3-year study treatment period at DCO was low (12% vs. 10% of patients receiving osimertinib vs. placebo), although the compliance rates were high (≥85% across both arms). As the analysis was designed to assess the impact on QoL of adjuvant treatment, data were not collected beyond recurrence, so provided

limited understanding on how a delay in recurrence with adjuvant osimertinib versus placebo impacts HRQoL in the longer term. Collection of long-term HRQoL data after disease recurrence could have provided useful information for payers, cost-effectiveness assessments, and regulatory bodies. On the other hand, interpretation of post-recurrence HRQoL data could be confounded by subsequent treatments and crossover to open-label osimertinib. Finally, the number of patients included in the analysis decreased over the course of the study with 40%–53% of patients included in the analysis at Week 96 compared with baseline.

Conclusions

In summary, HRQoL via the SF-36 survey was maintained during adjuvant osimertinib treatment in patients with stage IB–IIIA *EGFR*m NSCLC, who were disease-free following complete resection and prior adjuvant chemotherapy, if indicated. These results are in line with the overarching goal of adjuvant treatment, which is to treat with curative intent, while maintaining patients' HRQoL (19). Coupled with the significant DFS benefit and long-term safety profile observed with adjuvant osimertinib versus placebo in this patient population (13), these HRQoL data further support adjuvant osimertinib as an effective new treatment strategy in this setting.

Authors' Disclosures

M. Majem reports speakers bureau and advisory board fees from Sanofi, Pfizer, Janssen, Bristol-Myers Squibb, MSD, Boehringer-Ingelheim, AstraZeneca, Roche, Kyowa Kyrin, Pierre Fabre, Takeda Pharmaceutical, and Bayer AG and has received a research grant from Bristol-Myers Squibb outside the submitted work. J.W. Goldman reports research grants from AbbVie Inc., Merck & Co., Bristol-Myers Squibb, and AstraZeneca; speakers bureau fees from Merck & Co.; and honoraria from AstraZeneca outside the submitted work. T. John reports advisory board and consultancy fees from Roche AG, Bristol-Myers Squibb, Merck & Co., Ignyta, AstraZeneca, Takeda Pharmaceutical, MSD, Specialised Therapeutics, and Pfizer Inc. outside the submitted work. C. Grohe reports speakers bureau fees, advisory board fees, and honoraria from AstraZeneca, Boehringer-Ingelheim, and MSD and travel and accommodation fees from Boehringer-Ingelheim outside the submitted work. K. Laktionov reports speakers bureau fees, advisory board fees, and honoraria from AstraZeneca, Bristol-Myers Squibb, MSD, Roche, and Biocad; advisory board fees from Pfizer; and research grants from AstraZeneca outside the submitted work. S.-W. Kim reports speakers bureau and advisory board fees from Boehringer-Ingelheim; advisory board fees from AstraZeneca, Bristol-Myers Squibb, Eli Lilly & Co., and Novartis; and financial support from AstraZeneca outside the submitted work. T. Kato reports speakers bureau fees, advisory board fees, and research grants from AstraZeneca, Amgen Inc., Chugai Pharmaceutical Co., Ltd, Eli Lilly & Co., Merck Biopharma, MSD, and Pfizer Inc.; speakers bureau fees from Bristol-Myers Squibb, Novartis, Taiho Pharmaceutical, Boehringer-Ingelheim, and Roche AG; advisory board fees from Daiichi-Sankyo; speakers bureau and research grants from Novartis; and research grants from AbbVie Inc. outside the submitted work, as well as employment with Regeneron (spouse) and Eli Lilly & Co. S. Lu reports speakers bureau fees, advisory board fees, and research grants from AstraZeneca and Roche; speakers bureau fees from Hansoh; advisory board fees and research grants from Hutchison MediPharma; advisory board fees from Boehringer-Ingelheim, Simcere, ZaiLab, and GenomiCare; and research grants from Bristol-Myers Squibb, Heng, and Rui outside the submitted work. F. de Marinis reports advisory board and consultancy fees from Roche AG, Bristol-Myers Squibb, AstraZeneca, and MSD outside the submitted work. L. Bonanno reports speakers bureau fees from Roche, Bristol-Myers Squibb, and MSD and advisory board fees and a research grant from AstraZeneca. M. Domine reports speakers bureau, advisory board, and consultancy fees from AstraZeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, MSD, Pfizer Inc., and Roche AG outside the submitted work. F.A. Shepherd reports ownership of stock interest in AstraZeneca. S. Atagi reports honoraria from AstraZeneca, Eli Lilly, Ono, Taiho Pharmaceutical Co Ltd, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, Hisamitsu, MSD, Chugai, Kyowa Hakko Kirin, Merck, Novartis Pharma, and Thermo Fisher Scientific and research grants from AstraZeneca, Eli Lilly, Ono, Taiho Pharmaceutical Co Ltd, Boehringer Ingelheim, Pfizer, Bristol-Myers Squibb, MSD, Chugai, Merck, and F. Hoffmann-La Roche. L. Zeng reports ownership of stock interest and is an employee of AstraZeneca. N. Medic is an employee of AstraZeneca. D. Kulkarni reports ownership of stock interest and is an employee of AstraZeneca. M. Tsuboi reports advisory board fees from AstraZeneca, MSD, and Novartis and honoraria from Johnson & Johnson Japan, AstraZeneca KK, Eli Lilly Japan, Chugai Pharmaceutical Co., Ltd, Taiho Pharmaceutical, Medtronic Japan, Ono Pharmaceutical Co., Ltd, MSD, Bristol-Myers Squibb KK, and Teijin Pharma outside the submitted work. R.S. Herbst reports personal fees from AbbVie Inc., ARMO Biosciences, Biodesix, Bolt Biotherapeutics, Bristol-Myers Squibb, EMD Serono, Genmab, Halozyme, Heat Biologics, IMAB Biopharma, Immunocore, Infinity Pharmaceuticals, Loxo Oncology, Mirati Therapeutics, Nektar, Neon Therapeutics, NextCure, Novartis, Pfizer, Sanofi, Seattle Genetics, Shire PLC, Spectrum Pharmaceuticals, Symphogen, Takeda Pharmaceutical, Tesaro, Tocagen, Cybrexa, and Oncternal Therapeutics; personal fees and research grants from AstraZeneca, Eli Lilly & Co., Genentech/Roche, and Merck & Co.; and advisory board fees from Junshi Pharmaceuticals outside the submitted work. Y.-L. Wu reports personal fees and research grants from AstraZeneca, Bristol-Myers Squibb, Pfizer Inc., and Roche AG and personal fees from Boehringer-Ingelheim, Eli Lilly & Co., MSD, and Sanofi outside the submitted work. No disclosures were reported by the other authors.

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