

6.04 OSIMERTINIB, Tablet 40 mg, Tablet 80 mg, Tagrisso[®], AstraZeneca Pty Ltd.

1 Purpose of submission

- 1.1 The Category 2 submission requested a Section 85 (General Schedule), Authority Required Pharmaceutical Benefits Scheme (PBS) listing for osimertinib in combination with cisplatin or carboplatin, and pemetrexed for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with evidence in tumour material of an activating epidermal growth factor receptor mutation (*EGFRm*) known to confer sensitivity to EGFR tyrosine kinase inhibitors (TKIs).
- 1.2 While the submission did not specify the type of *EGFRm* in the wording of the request, it referred to exon 19 deletions or exon 21 L858R substitution mutations, as specified in the TGA indication and the inclusion criteria of the pivotal FLAURA2 trial.
- 1.3 Listing was requested on the basis of a cost-effectiveness analysis versus osimertinib monotherapy. The key components of the clinical issue addressed by the submission are presented in Table 1.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	First-line treatment of patients with locally advanced (Stage IIIB/C) or metastatic (Stage IV) <i>EGFRm</i> NSCLC
Intervention	Osimertinib 80 mg once daily, in combination with pemetrexed (500 mg/m ² ; with vitamin supplementation) plus either cisplatin (75 mg/m ²) or carboplatin (AUC5), with both treatments administered every three weeks for four cycles, followed by osimertinib 80 mg once daily, plus pemetrexed maintenance (500 mg/m ²) every three weeks.
Comparator	Osimertinib monotherapy 80 mg once daily
Outcomes	Primary outcome: PFS Key secondary outcomes: OS, ORR, DoR, depth of response, DCR, post-progression outcomes, HRQoL Safety
Clinical claim	In patients with locally advanced or metastatic <i>EGFRm</i> NSCLC, osimertinib in combination with platinum plus pemetrexed chemotherapy is superior in terms of effectiveness compared with osimertinib monotherapy. In patients with locally advanced or metastatic <i>EGFRm</i> NSCLC, osimertinib in combination with platinum plus pemetrexed chemotherapy is associated with inferior but manageable safety compared with osimertinib monotherapy.

Source: Table 1, pp 15-16 of the submission

DCR = disease control rate; DoR = duration of response; *EGFRm* = epidermal growth factor receptor-mutated; HRQoL = health related quality of life; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; SoC = standard of care; TKI = tyrosine kinase inhibitor.

2 Background

Registration status

- 2.1 Osimertinib plus chemotherapy (pemetrexed and platinum-based chemotherapy) (O+C) was approved by the Therapeutic Goods Administration (TGA) on 30 October 2024 for “the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 L858R mutations.”
- 2.2 The August 2024 Advisory Committee on Medicines (ACM) decision advised that the data from FLAURA2 did not support the use of O+C where there is neither exon 19 deletion or exon 21 L858R substitution mutations.
- 2.3 Based on the current TGA approved product information (dated 2 December 2024), osimertinib (as monotherapy) is TGA registered in Australia for the following indications:
 - As adjuvant therapy after tumour resection in patients with NSCLC whose tumours have activating *EGFRm*, as detected by a validated test.
 - The treatment of patients with locally advanced, unresectable (stage III) NSCLC whose tumours have activating EGFR mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy.
 - For the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have activating *EGFRm*, as detected by a validated test.
 - For the treatment of patients with locally advanced or metastatic NSCLC that is EGFR T790M mutation positive, as detected by a validated test.

Previous PBAC consideration

- 2.4 The Pharmaceutical Benefits Advisory Committee (PBAC) has not previously considered O+C for this indication.
- 2.5 The PBAC recommended osimertinib (as monotherapy) for the second-line treatment of locally advanced or metastatic (stage IIIB or IV) *EGFRm* NSCLC at the November 2018 meeting¹ (following earlier considerations in November 2017 and July 2018).
- 2.6 Osimertinib (as monotherapy) for the first-line treatment of locally advanced or metastatic (stage IIIB or IV) *EGFRm* NSCLC was recommended at the July 2020 PBAC meeting² (following consideration in July 2019).

¹ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2018-11/Osimertinib-psd-november-2018>

² <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2020-07/osimertinib-tablet-40-mg-tablet-80-mg-tagrisso>

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- 2.7 The PBAC recommended osimertinib (as monotherapy) for the treatment of Stage IB to IIIA *EGFR* positive NSCLC as adjuvant therapy after surgical resection at the November 2023 PBAC meeting³.
- 2.8 The PBAC noted amivantamab and lazertinib, a treatment proposed for a similar population to O+C, was not recommended at the March 2025 PBAC meeting⁴.

3 Requested listing

- 3.1 Secretariat suggestions and additions proposed are shown in italics and deletions are in strikethrough.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price Max Qty (DPMQ)	Max. qty packs	Max. qty units	No. of Rpts	Available brands
OSIMERTINIB					
osimertinib 80 mg tablet, 30	DPMQ-Published: \$7,582.10 DPMQ-Effective: \$█ (SPA)	1	30	5-2	Tagrisso
osimertinib 40 mg tablet, 30	DPMQ-Published: \$7,582.10 DPMQ-Effective: \$█ (SPA)	1	30	5	
Category / Program: GENERAL - General Schedule (Code GE)					
Prescriber type: Medical Practitioners					
Restriction type: Authority Required (Immediate assessment)					
Administrative Advice: No increase in the maximum quantity of number of units may be authorised.					
Administrative Advice: No increase in the maximum number of repeats may be authorised.					
Administrative Advice: Special Pricing Arrangements apply.					
Administrative Advice: <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>					
Indication: <i>Locally advanced (Stage IIIB/C) or metastatic (Stage IV) non-small cell lung cancer Stage IIIB/IIIC (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)</i>					
Treatment Phase: <i>Initial treatment as first-line epidermal growth factor receptor tyrosine kinase inhibitor therapy (combination therapy)</i>					
Clinical criteria:					
Patient must have a WHO performance status of 2 or less,-					
AND					
Clinical criteria:					
Treatment is in combination with cisplatin/carboplatin and pemetrexed for a maximum of four cycles. <i>The treatment must be in combination with platinum-based chemotherapy (PBC) plus pemetrexed for a maximum of four cycles (12 weeks), unless intolerance of a severity necessitating treatment withdrawal had occurred to any of these agents. The details of intolerance must be documented in the patient's medical record.</i>					
AND					

³ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2023-11/osimertinib-tagrisso-PSD-Nov-2023>

⁴ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-made-by-the-pbac-march-2025>

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Clinical criteria:
Patient must not have previously received PBS-subsidised treatment with these drugs for this condition, <i>Patient must not have previously received PBS-subsidised treatment with this drug, platinum-based chemotherapy and pemetrexed for this condition</i>
AND
Clinical criteria:
Patient must not have received previous PBS-subsidised treatment with another epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI); <i>or OR</i>
Patient must have developed intolerance to another epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) of a severity necessitating permanent treatment withdrawal.
Population criteria:
Patient must have evidence in tumour material of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors.
Prescribing Instructions:
PBS-subsidised treatment with this drug is restricted to one line of therapy at any disease staging for NSCLC (i.e. if therapy has been prescribed for early disease, subsidy under locally advanced or metastatic disease is no longer available).

Category / Program: GENERAL - General Schedule (Code GE)
Prescriber type: Medical Practitioners
Restriction type: Authority Required (Immediate assessment)
Administrative Advice: No increase in the maximum quantity of number of units may be authorised.
Administrative Advice: No increase in the maximum number of repeats may be authorised.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: <i>Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.</i>
Indication: Locally advanced (Stage IIIB/C) or metastatic (Stage IV) non-small cell lung cancer <i>Stage IIIB/IIIC (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)</i>
Treatment Phase: Continuing treatment of first-line EGFR tyrosine kinase inhibitor therapy (<i>combination therapy</i>)
Clinical criteria:
Treatment is in combination with pemetrexed, <i>Treatment must be in combination with pemetrexed unless intolerance of a severity necessitating treatment withdrawal had occurred. The details of intolerance must be documented in the patient's medical record.</i>
AND
Clinical criteria:
Patient must have previously received PBS-subsidised treatment with osimertinib in combination with cisplatin/carboplatin and pemetrexed for this condition, <i>Patient must have previously received PBS-subsidised treatment with this drug in combination with platinum-based chemotherapy and pemetrexed for this condition,</i>
AND
Clinical criteria:
Patient must not have developed disease progression while receiving treatment with this drug for this condition.
Treatment criteria:
<i>Patient must be undergoing continuing treatment with this drug as first-line combination therapy (i.e. there are 3 Continuing treatment listings for this drug - ensure the correct Continuing treatment restriction is being accessed).</i>
Population criteria:
Prescribing Instructions:
PBS-subsidised treatment with this drug is restricted to one line of therapy at any disease staging for NSCLC (i.e. if therapy has been prescribed for early disease, subsidy under locally advanced or metastatic disease is no longer available).

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- 3.2 The submission requested a Section 85 (General Schedule) Authority Required (telephone/online) PBS listing of osimertinib for use in combination with chemotherapy for the first-line treatment of patients with locally advanced (Stage IIIB/C) or metastatic (Stage IV) *EGFRm* NSCLC. The current PBS listings for osimertinib in first- and second-line NSCLC, do not refer to Stage IIIC. Stage IIIC is a newly defined group in the tumour-node-metastasis (TNM) classification 8th edition, which includes patients with large tumours (T3 or T4) and N3 disease. Patients that are now classified as Stage IIIC would have been considered as Stage IIIB under the previous classification.
- 3.3 The submission proposed three sets of criteria: 1) initiation of treatment in combination with either cisplatin or carboplatin, and pemetrexed; 2) continuation of treatment in combination with pemetrexed; and 3) continuation of treatment without pemetrexed. The third set would allow patients to continue osimertinib where maintenance pemetrexed has ceased due to intolerance.
- 3.4 The TGA recommended dose of osimertinib is 80 mg once daily, until disease progression or unacceptable toxicity. A 40 mg dose is also available for patients who may require dose reduction, and flat pricing across the doses was proposed, consistent with the pricing structure of osimertinib in other PBS indications.
- 3.5 Osimertinib is proposed for use in combination with cisplatin or carboplatin, and pemetrexed. These chemotherapies are included in the Efficient Funding of Chemotherapy (EFC) Schedule as unrestricted benefit listings.
- 3.6 The current PBS listing for osimertinib in first-line NSCLC includes an eligibility criterion that states “The treatment must be the sole PBS-subsidised therapy for this condition”. As such, patients would not be eligible for PBS-subsidised chemotherapy, in combination with osimertinib, under the current PBS item. Due to the relatively low cost of cisplatin/carboplatin, and pemetrexed, the ESC noted patients are already able to access osimertinib in combination with chemotherapy, where chemotherapy is funded by either hospitals or patients. The Pre-Sub Committee Response (PSCR) stated that the proposed PBS listing was not for all osimertinib patients but only for a proportion (estimated as █████%) who are suitable candidates able to tolerate the additional toxicity to obtain the significant PFS improvement and possible OS gain.
- 3.7 The proposed listing for O+C included a clinical criterion for continuing treatment of first-line EGFR-TKI therapy (osimertinib), as monotherapy, where maintenance pemetrexed has ceased due to intolerance. This was consistent with the FLAURA2 trial.
- 3.8 The submission requested a Special Pricing Arrangement (SPA) for this indication, with a confidential effective approved ex-manufacturer price (AEMP) of \$████ and dispensed price for maximum quantity (DPMQ) of \$████. The effective AEMP of osimertinib (80 mg or 40 mg, 30 tablets) is \$████ as monotherapy in the first-line setting.

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- 3.9 The proposed population criteria were consistent with those for other EGFR-TKIs (erlotinib, gefitinib and afatinib). However, the proposed population criterion for O+C ('patient must have evidence in tumour material of an activating epidermal growth factor receptor (EGFR) gene mutation known to confer sensitivity to treatment with EGFR tyrosine kinase inhibitors') was broader than the TGA indication and the inclusion criteria of the pivotal trial (FLAURA2). The TGA indication and inclusion criteria of FLAURA2 specify the treatment of patients with the *EGFRm* exon 19 deletions or exon 21 L858R substitution mutations, while the proposed PBS listing does not specify the specific *EGFRm*. This absence of mention of the specific *EGFRm* was consistent with the current PBS listings for osimertinib in the adjuvant and first-line setting, while treatment is limited to patients with evidence of EGFR T790M mutation in tumour material in the second-line setting (consistent with the TGA indications, see paragraphs 2.1 and 2.22.3).
- 3.10 The proposed criterion for continuing treatment with O+C, 'Patient must not have developed disease progression while receiving treatment with these drugs for this condition' was not consistent with FLAURA2. In FLAURA2, patients who progressed on O+C or osimertinib monotherapy were permitted to continue treatment if they were deemed to be continuing to derive clinical benefit. At data cut off 1 (DCO1) April 2023, 81/95 (85%) continued osimertinib treatment beyond progression in the O+C arm compared to 133/158 (84%) in the osimertinib arm for a median duration of 1.84 and 1.94 months, respectively. Additionally, 9.7% of patients in the O+C arm were still on pemetrexed treatment beyond disease progression. This calls into question the applicability of the FLAURA2 evidence to the proposed PBS listing (which would require cessation of PBS subsidised therapy at progression) and is discussed in paragraphs 6.17 and 6.18. However, the PBAC has previously accepted a similar discord between trial practice (treatment beyond progression) and the proposed PBS listing (absence of progression to qualify for continuing treatment) with respect to the PBS listing of osimertinib monotherapy (see paragraph 6.18).
- 3.11 The submission acknowledged that the proposed restriction specifying the use of O+C in patients with a WHO score of 2 or less was inconsistent with FLAURA2 where only patients with a WHO score of 0 and 1 were included. However, the submission justified the proposed restriction based on previous PBAC recommendations for other EGFR-TKIs (including osimertinib monotherapy) for the same population, where the PBAC recommended restrictions for patients with WHO score of 2 or less, despite the trial evidence including patients with WHO scores of 0 and 1. This was in contrast to the submission's discussion which stated that O+C would be more acceptable for patients who are suitable candidates for more 'intense treatment' and that 'suitable patients' would include those with good performance status (WHO PS=0-1) who are also expected to have acceptable tolerability for chemotherapy. However, ESC noted there is high level of toxicity related to O+C (paragraph 6.376.37), and therefore it may be appropriate for the proposed PBS restriction to match the trial with respect WHO performance status. The Pre-PBAC response acknowledged changing the WHO score

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in the proposed restriction to 0-1 (aligned with FLAURA2), would be a further signal to clinicians that this regimen is not suitable for all patients.

- 3.12 The submission stated that grandfathering provisions were not required. However, the submission assumed that in the period between TGA registration and PBS listing of the O+C regimen, the use of osimertinib will increase with some patients funding the chemotherapy privately (as mentioned in paragraph 3.5), and that upon PBS listing of O+C these patients will 'switch' to the PBS-subsidised O+C regimen (see paragraph 6.54). The submission stated that following publication of the FLAURA2 pivotal trial and TGA registration, many Australian patients are likely to be administered concomitant platinum and/or pemetrexed therapy with osimertinib, despite this usage being outside the current osimertinib monotherapy PBS restriction (as discussed in paragraph 3.6). The submission estimated that < 500 prevalent patients will commence O+C before the PBS listing.
- 3.13 The submission proposed 5 repeats for both initial and continuing treatment, which would provide approximately 6-months supply, consistent with other PBS indications for osimertinib. The Secretariat proposed reducing the number of repeats for the initial restriction from 5 to 2 to align with the initial chemotherapy treatment which is to be administered every three weeks for four cycles (12 weeks in total). The PSCR stated the sponsor accepted the Secretariat's recommendation to reduce the number of repeats for the initial treatment criteria (from 5 to 2). The sponsor also accepted the removal of the 40 mg dose from the initial restriction (aligned with other osimertinib restrictions).
- 3.14 The Secretariat noted that it might be feasible to combine the current osimertinib monotherapy listing with the proposed combination therapy, under the same existing item codes by removing the clinical criterion "The treatment must be the sole PBS-subsidised therapy for this condition".

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

4 Population and disease

- 4.1 NSCLC is the most common type of lung cancer, representing approximately 85% of all diagnoses. For patients with locally advanced or metastatic (Stage IIIB/C–IV) NSCLC, treatment goals are to maintain, or improve, health-related quality of life (HRQoL), and to prolong both progression-free survival (PFS) and overall survival (OS). In this setting, first-line treatment typically consists of systemic therapy, with choice of systemic therapy based on biomarker status (e.g., mutation or PD-L1 expression). Currently in Australia, for patients with locally advanced or metastatic NSCLC who are not amenable to curative surgery or radiotherapy, and whose tumours harbour *EGFRm*, the first-line standard of care (SoC) consists of treatment with EGFR-TKIs.
- 4.2 *EGFRm* are one of the most common activating pathway events (genetic mutations which accelerate cancer progression) in NSCLC. In Australia, *EGFRm* accounts for 12% to 36% of NSCLC and confer sensitivity to EGFR-TKIs. The PBAC and the Medical

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Services Advisory Committee (MSAC) in their previous considerations noted that exon 19 deletion or exon 21 L858R substitution mutations account for about 70% of detected *EGFRm* (para 3.3, osimertinib Public Summary Document [PSD], November 2023 PBAC meeting).

- 4.3 Osimertinib is orally administered and is a selective and irreversible inhibitor of EGFRs harbouring single (L858R or del746-750) or double (L858R/T790M or del746-750/T790M) mutations.
- 4.4 The submission proposed osimertinib in combination with cisplatin/carboplatin and pemetrexed chemotherapy, as an alternative regimen to osimertinib monotherapy, that would be considered for patients who are suitable candidates for more intense treatment. The submission stated that suitable patients include those with good performance status (WHO PS=0-1) who are also expected to have acceptable tolerability for chemotherapy (see paragraph 3.11). The submission also proposed that O+C offers a more efficacious treatment option to optimise outcomes for patients with *EGFRm* NSCLC with the greatest level of unmet need, such as patients with CNS metastases, challenging tumour mutations such as exon 21 L858R substitution mutations and/or those with higher tumour burden.

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

5 Comparator

- 5.1 The submission nominated osimertinib as the main comparator for O+C. The main arguments provided in support of this nomination were:
- Based on 10% PBS sample data, approximately 90% of the NSCLC *EGFRm* population is currently treated with osimertinib (out of all the PBS-listed EGFR TKIs), hence it is the therapy most likely to be replaced by O+C in clinical practice once listed.
 - Osimertinib was also recommended by previous clinical guidelines as the preferred first-line treatment for locally advanced/metastatic *EGFRm* NSCLC^{5,6}.
- 5.2 The nomination of osimertinib as the comparator for O+C for this population was appropriate. However, as discussed in paragraph 6.54, due to the relatively low cost of cisplatin/carboplatin, and pemetrexed, ESC noted patients are already able to access O+C, where it is funded by either hospitals or patients. Amivantamab plus lazertinib (A+L) was not recommended at the March 2025 PBAC meeting⁷ for a similar population and is therefore a potentially relevant near-market comparator.

⁵ Hendriks, L. E., et al. 2023. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*, 34(4), 339-357.

⁶ Riely, G., et al. 2024. Non-Small Cell Lung Cancer, Version 4.2024, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*, 22, 249-274.

⁷ <https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-made-by-the-pbac-march-2025>

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals with the health condition (3), family members or interested members of the general public (5) and organisations (4) via the Consumer Comments facility on the PBS website. The PBAC noted the comments from individuals and family members who are currently treated with osimertinib monotherapy, sharing their treatment experience and expressing the need to access O+C as an additional treatment option to treat *EGFRm* NSLC. All consumer input was supportive of a PBS listing.
- 6.3 The Lung Foundation Australia noted the negative impact of lung cancer diagnosis on individuals' mental health and wellbeing and the importance of new treatment options to improve prognosis.
- 6.4 Rare Cancer Australia (RCA) noted side effects of current treatment for NSCLC have a negative impact on individuals' quality of life. RCA further noted the challenges for patients receiving treatment for NCSLC to maintain employment and may lead to financial stress when self-funding non-PBS listed treatments. RCA further noted the increased toxicity associated with the O+C therapy versus osimertinib monotherapy.
- 6.5 The Thoracic Oncology Group of Australasia (TOGA) referenced FLAURA2 in terms of O+C outcome of improved PFS and an observed trend towards OS benefit compared to osimertinib monotherapy. It noted chemotherapy is both inexpensive and widely accessible for all individuals living with EGFR+ advanced NSCLC and the increased toxicity was as expected from the addition of chemotherapy. TOGA also noted molecular profiling data within the FLAURA2 trial illustrated many patients with activating *EGFRm* harbour co-mutations that affect response and prognosis. The addition of chemotherapy in FLAURA2 partially mitigates against these co-mutations, resulting in better outcomes for patients. TOGA noted that not all patients will be fit enough for nor accepting of having the combination of osimertinib and chemotherapy.
- 6.6 The Medical Oncology Group of Australia Incorporated (MOGA) also expressed its strong support for the O+C submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the FLAURA2 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for 3 (out of a maximum of 5, where 5 and 4

represent the grades with substantial improvement)⁸, based on a comparison with osimertinib monotherapy.

Clinical trial

6.7 The submission was based on one ongoing head-to-head randomised controlled trial (RCT), FLAURA2 (N = 557), comparing the efficacy and safety of O+C to osimertinib as first-line treatment in patients with locally advanced or metastatic NSCLC with evidence of an *EGFRm* (specifically, exon 19 deletion or exon 21 L858R substitution mutations).

6.8 Details of the trial presented in the submission are provided in Table 2.

Table 2: Studies presented in the submission

Study ID	Reports	Citation
FLAURA2 NCT04035486	FLAURA2 Clinical Study Report Interim Analysis DCO 03 April 2023	A Phase III, Open-label, Randomised Study of osimertinib With or Without Platinum Plus Pemetrexed Chemotherapy, as First-line Treatment in Patients with Epidermal Growth Factor Receptor Mutation Positive, Locally Advanced or Metastatic Non-small Cell Lung Cancer
	FLAURA2 Interim analysis DCO 8 January 2024: 4O First-line (1L) osimertinib (osi) ± platinum-pemetrexed in EGFR-mutated (EGFRm) advanced NSCLC: FLAURA2 post-progression outcomes	Valdiviezo, N, et al. (2024). 4O First-line (1L) osimertinib (osi) ± platinum-pemetrexed in EGFR-mutated (EGFRm) advanced NSCLC: FLAURA2 post-progression outcomes. ESMO Open. 9. 102583. 10.1016/j.esmoop.2024.102583.
	Main publication	
	Osimertinib with or without chemotherapy in EGFR-mutated advanced NSCLC	Planchard D et al. (2023). Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. N Engl J Med. 2023 Nov 23;389(21):1935-1948. doi: 10.1056/NEJMoa2306434. Epub 2023 Nov 8. PMID: 37937763.
	Abstracts and other publications:	
Phase III, Open-Label, Randomized Study of osimertinib with or without Platinum Plus Pemetrexed Chemotherapy, as First-Line Treatment in Patients with Epidermal Growth Factor Receptor (EGFR) Mutation - Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer (FLAURA2)	Jänne, P., et al. (2023). PL03.13 Osimertinib With/Without Platinum-Based Chemotherapy as First-line Treatment in Patients with EGFRm Advanced NSCLC (FLAURA2). Journal of Thoracic Oncology, 18, S36-S37.	
514MO Acquired mechanisms of resistance to first-line (1L) osimertinib with or without platinum-based chemotherapy (CT) in EGFR-mutated (EGFRm) advanced NSCLC: Preliminary data from FLAURA2	Lee, C. K., et al. (2023). 514MO Acquired mechanisms of resistance to first-line (1L) osimertinib with or without platinum-based chemotherapy (CT) in EGFR-mutated (EGFRm) advanced NSCLC: Preliminary data from FLAURA2. Annals of Oncology, 34, S1669-S1670.	

⁸ Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017.

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Study ID	Reports	Citation
	CNS Efficacy of Osimertinib With or Without Chemotherapy in Epidermal Growth Factor Receptor-Mutated Advanced Non-Small-Cell Lung Cancer	Jänne PA, et al. (2024). CNS Efficacy of Osimertinib With or Without Chemotherapy in Epidermal Growth Factor Receptor-Mutated Advanced Non-Small-Cell Lung Cancer. <i>J Clin Oncol.</i> 2024 Mar 1;42(7):808-820. doi: 10.1200/JCO.23.02219. Epub 2023 Dec 2. PMID: 38042525; PMCID: PMC10906563.
	Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC	Planchard D, et al. (2023). FLAURA2 Investigators. Osimertinib with or without Chemotherapy in EGFR-Mutated Advanced NSCLC. <i>N Engl J Med.</i> 2023 Nov 23;389(21):1935-1948. doi: 10.1056/NEJMoa2306434. Epub 2023 Nov 8. PMID: 37937763.
	First-line (1L) osimertinib (osi) ± platinum-pemetrexed in patients (pts) with EGFRm advanced NSCLC: FLAURA2 China cohort	Cheng, Yuchen & Fan, et al. (2023). 562P First-line (1L) osimertinib (osi) ± platinum-pemetrexed in patients (pts) with EGFRm advanced NSCLC: FLAURA2 China cohort. <i>Annals of Oncology.</i> 34. S1689. 10.1016/j.annonc.2023.10.640.
	512MO FLAURA2: safety and CNS outcomes of first-line (1L) osimertinib (osi) ± chemotherapy (CTx) in EGFRm advanced NSCLC	Planchard D, et al. (2023). 512MO FLAURA2: safety and CNS outcomes of first-line (1L) osimertinib (osi) ± chemotherapy (CTx) in EGFRm advanced NSCLC. <i>Annals of oncology</i> 2023; 34(null): S1668.
	Exposure response and safety analysis of osimertinib in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of locally advanced or metastatic NSCLC patients with EGFRm (FLAURA2)	Yang J, et al. (2024). Exposure response and safety analysis of osimertinib in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of locally advanced or metastatic NSCLC patients with EGFRm (FLAURA2). <i>Cancer research</i> 2024; 84(7): null.
	FLAURA2: Impact of tumour burden on outcomes of first-line osimertinib + chemotherapy in patients with EGFR-mutated advanced NSCLC	Valdiviezo, N., et al. (2024). FLAURA2: Impact of tumour burden on outcomes of first-line osimertinib + chemotherapy in patients with EGFR-mutated advanced NSCLC. 2024 World Conference on Lung Cancer.
	FLAURA2: Resistance, and impact of baseline TP53 alterations in patients treated with first-line osimertinib with or without platinum-pemetrexed	Yang, J. et al. (2024). FLAURA2: Resistance, and impact of baseline TP53 alterations in patients treated with first-line osimertinib with or without platinum-pemetrexed. 2024 World Conference on Lung Cancer.

Source: Table 10, p 37- 42 of the submission.

CSR = clinical study report; CNS = central nervous systems; CT = chemotherapy; CTx = chemotherapy; DCO = data cutoff; EGFRm = Epidermal growth factor receptor mutation; Non-sq = non squamous; NSCLC = non-small cell lung cancer; Osi = osimertinib; pts = patients; SRI = safety run in.

6.9 The key features of FLAURA2 are summarised in Table 3.

6.10 FLAURA2 is currently ongoing with the final analysis of OS to be conducted when OS data is approximately 60% mature. Given it is event driven, there is no predefined date by when final reporting of OS will occur, but it is anticipated that this will be during the first half of 2026 (TGA Delegate’s Overview). The submission presented results from 2 clinical DCOs:

- First interim primary analysis DCO1 (April 2023) reported for PFS, OS and other key secondary efficacy outcomes.

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- Second interim OS analyses DCO2 (January 2024) reported updated OS data (40.6% maturity). DCO2 was an additional data cut to assess OS and subsequent treatments at the request of the FDA.

6.11 The submission based its clinical claim on the primary outcome, PFS, from DCO1, 3 April 2023, and the secondary outcome, OS, from both DCO1 April 2023 and DCO2 January 2024.

Table 3: Key features of the included evidence

Trial	N	Design	Risk of bias	Patient population	Outcomes	Use in modelled evaluation
O+C versus osimertinib						
FLAURA2	557	MC, RCT. Both treatment arms were open label	Low	Locally advanced or metastatic NSCLC treatment naïve for advanced disease EGFR exon 19del or exon 21 L858R disease	Primary: PFS (INV) Secondary: OS, ORR, DOR, Depth of response, DCR, PRO: EORTC QLQ-30 and EORTC QLQ-LC13 Exploratory sensitivity analysis: PFS (BICR) Post progression outcomes: PFS2, TFST, TSST	OS, PFS, TTTD, EQ-5D-5L

Source: Figure 2.3, p 45 of the submission, Section 2.5 of the submission, Section 3.4 of the submission
BICR = blinded independent central review; DCR = disease control rate; DOR = duration of response; EGFR = epidermal growth factor receptor; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level Version; HRQoL = health related quality of life; INV = investigator assessment; MC = multi centre; NSCLC = non-small cell lung cancer; N = number of patients; OS = overall survival; O+C = osimertinib plus chemotherapy; PFS = progression free survival; PFS2 = progression-free survival after first subsequent therapy; PRO = patient reported outcome; RCT = randomised control trial; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy; TTTD = time to treatment discontinuation.

Comparative effectiveness

Primary outcome (PFS)

6.12 Results of PFS based on the investigator assessment, from the full analysis set (FAS) population at DCO1, are presented in Table 4 and the corresponding Kaplan-Meier (KM) curve is presented in Figure 1.

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Table 4: Progression-free survival by Investigator assessment (randomised period – FAS; DCO1: 3 April 2023)

	O+C N = 279	Osimertinib N = 278
Progression total n (%)	120 (43.0%)	166 (59.7%)
RECIST progression n (%) ^a	95 (34.1%)	158 (56.8%)
Death n (%) ^b	25 (9.0%)	8 (2.9%)
Time to event (months)		
Median PFS (95% CI)	25.5 (24.7, NC)	16.7 (14.1, 21.3)
PFS rate at 6 months (%) (95% CI) ^c	90.7 (86.6, 93.6)	83.5 (78.6, 87.4)
PFS rate at 12 months (%) (95% CI) ^c	79.7 (74.3, 84.1)	65.5 (59.5, 70.8)
PFS rate at 18 months (%) (95% CI) ^c	70.6 (64.7, 75.7)	48.5 (42.4, 54.3)
PFS rate at 24 months (%) (95% CI) ^c	57.2 (50.4, 63.3)	40.8 (34.7, 46.9)
Median (range) follow-up for PFS in all patients (months) ^d	19.5 (0, 33.3)	16.5 (0, 33.1)
p-value	< 0.0001	
Hazard ratio (95% CI)	0.62 (0.49, 0.79)	

Source: Table 18, pp86 – 87 of Attachment 2.2 of the Submission (CSR)

CI = confidence interval; FAS = full analysis set; N = number of patients; n = number of patients progressed; NC = not calculable; O+C = osimertinib plus chemotherapy; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours.

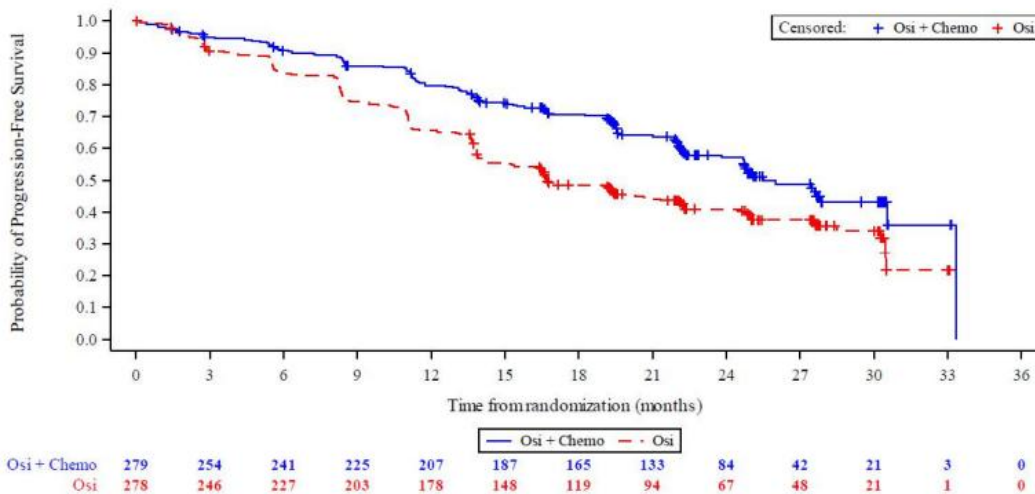
^a Only includes progression events that occur within 2 consecutive scheduled visits (plus visit window) of the last evaluable assessment (or randomisation).

^b Death in the absence of RECIST progression, within 2 visits of baseline or last RECIST assessment (Not Evaluable is not considered as missing visit).

^c Calculated using the KM method.

^d Calculated as the median, minimum, and maximum time from randomisation to date of progression or date of censoring in all patients.

Bold indicates a statistically significant difference. Figure 1: Kaplan -Meier plot of PFS (months) by investigator assessment (randomised period – FAS; DCO1: 3 April 2023)



Source: Figure 2.5, p 72 of the submission

DCO1 = data cut-off 1; FAS = full analysis set; Osi = osimertinib; Osi + Chemo = osimertinib plus chemotherapy; PFS = progression-free survival.

6.13 There was a statistically significant improvement in PFS for O+C compared to osimertinib with a hazard ratio [HR] of 0.62 ([95% CI: 0.49, 0.79]; p-value < 0.0001). Treatment with O+C resulted in a median PFS gain of 8.8 months (25.5 months median PFS in the O+C arm compared to 16.7 months median PFS in the osimertinib arm). The evaluation considered the difference was likely to be clinically meaningful; the American Society of Clinical Oncology (ASCO) have recommended targets for

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meaningful clinical trial goals to be 4 months for PFS⁹. The improvement in PFS was similar to that observed in the FLAURA trial of osimertinib monotherapy compared with standard care (SC) that supported the PBAC recommendation for monotherapy in July 2020 (median PFS was 18.9 months and 10.2 months in the osimertinib and SC arms respectively, corresponding to an absolute difference of 8.7 months, HR=0.46 [95% CI: 0.37, 0.57; p-value < 0.0001; Table 5 osimertinib PSD, July 2020 PBAC meeting).

Secondary outcome (OS)

- 6.14 Results of OS from DCO1 and DCO2 are summarised in Table 5. As reported in the submission, the OS data was immature at this data cut with only 26.8% events. The observed difference in OS for O+C over osimertinib was not statistically significant (HR=0.90 [95% CI: 0.65, 1.24], p=0.5238).
- 6.15 At DCO2, OS remained immature (41% events) with a non-statistically significant HR between O+C and osimertinib (HR=0.75 [95% CI: 0.57, 0.97, p=0.0280). The submission stated that a p-value of ≤ 0.000001 was required for statistical significance at this second interim analysis as agreed with the FDA. Median OS was not reached (95% CI: 38.0, not calculable [NC]) for O+C and was 36.7 months (95% CI 33.2, NC) for osimertinib. The corresponding KM curve for this data cut is presented in Figure 2.
- 6.16 The absolute difference in median OS could not be calculated due to data immaturity for FLAURA2. However, the improvement in OS appeared similar to that observed in the FLAURA trial of osimertinib monotherapy compared with SC (HR=0.799 [95% CI: 0.640, 0.996], p-value= 0.0462). In the FLAURA trial, median OS was 38.6 months and 31.8 months in the osimertinib and SC arms respectively, corresponding to an absolute difference of 6.8 months (Table 6 osimertinib PSD, July 2020 PBAC meeting).

⁹ Ellis, L. M., Bernstein, D. S., Voest, E. E., Berlin, J. D., Sargent, D., Cortazar, P., Garrett-Mayer, E., Herbst, R. S., Lilenbaum, R. C., Sima, C., Venook, A. P., Gonen, M., Schilsky, R. L., Meropol, N. J., & Schnipper, L. E. (2014). American Society of Clinical Oncology Perspective: Raising the bar for clinical trials by defining clinically meaningful outcomes. *Journal of Clinical Oncology*, 32(12), 1277–1280.

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Table 5: Overall survival (randomised period – FAS; DCO1: 3 April 2023 & DCO2: 8 January 2024)

	O+C N = 279	Osimertinib N = 278
DCO1 April 2023		
Death (n)%	71 (25.4%)	78 (28.1%)
Time to event (months)		
Median OS (95% CI)	NC (31.9, NC)	NC (NC, NC)
Median (range) follow-up for OS in all patients (months) ^b	23.9 (0.1, 34.1)	23.7 (0.1, 33.9)
p-value	0.5238	
Hazard ratio (95% CI)	0.90 (0.65, 1.24)	
DCO2 January 2024		
Death (n)%	100 (35.8%)	126 (45.3%)
Time to event (months)		
Median OS (95% CI)	NC (38.0, NC)	36.7 (33.2, NC)
p-value	0.0280	
Hazard ratio (95% CI)	0.75 (0.57, 0.97)	
OS rate at 6 months (%) (95% CI) ^a	93.5 (89.9, 95.9)	94.9 (91.6, 97.0)
OS rate at 12 months (%) (95% CI) ^a	88.8 (84.4, 92.0)	92.0 (88.1, 94.7)
OS rate at 18 months (%) (95% CI) ^a	85.5 (80.8, 89.2)	83.9 (79.0, 87.8)
OS rate at 24 months (%) (95% CI) ^a	79.7 (74.5, 84.0)	72.1 (66.4, 77.0)

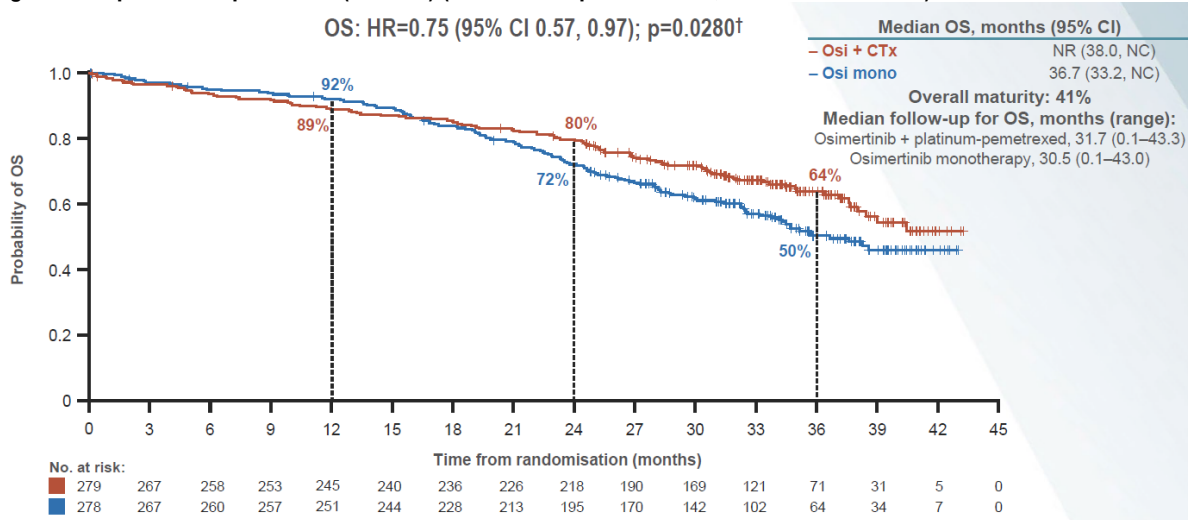
Source: Table 25, p 74 of the submission. Table 14.2.2.1b, p 2 of Attachment D5169C00001-FLAURA2-OS-IA-Tables-20240213 of the submission.

CI = confidence interval; FAS = full analysis set; N = number of patients; n = number of deaths; NC = not calculable; OS = overall survival.

^a calculated using the KM method.

^b Time from randomization to date of death or to date of censoring for censored patients.

Figure 2: Kaplan-Meier plot of OS (months) (randomised period – FAS; DCO2: 08 Jan 2024)



Source: Figure 2.8, p 76 of the submission

CI = confidence interval; CTx = chemotherapy; HR = hazard ratio; NC = not calculable; OS = overall survival; osi = osimertinib.

Note (†): p-value of ≤0.000001 was required for statistical significance at this second interim analysis as agreed by the FDA.

6.17 The survival advantage for O+C observed in FLAURA2 captured treatment beyond progression, noting that 81/95 (85%) continued osimertinib treatment beyond progression in the O+C arm compared to 133/158 (84%) in the osimertinib arm for a median duration of 1.84 and 1.94 months, respectively. This was inconsistent with the proposed PBS restriction. Given that the proposed PBS listing would limit continuing

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treatment to those who have not experienced disease progression, the observed OS outcomes may exceed what might be expected in clinical practice in Australia.

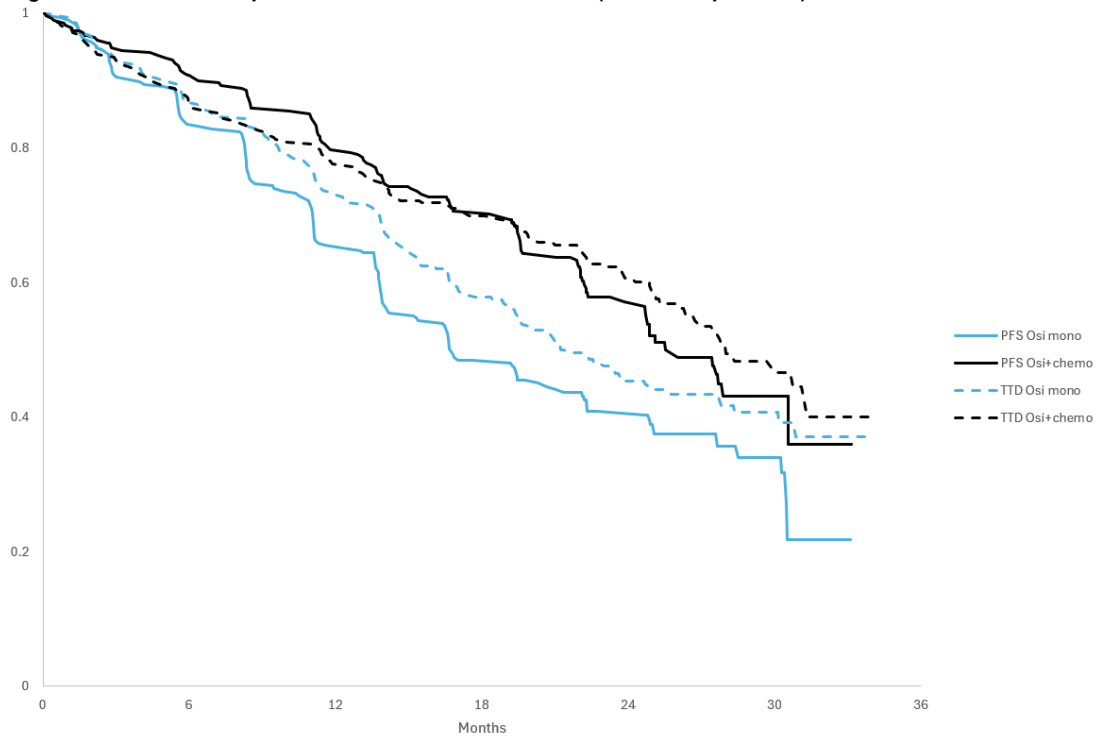
- 6.18 The submission stated that the clinical criteria seen in FLAURA2, that allowed for the continued use of O+C upon disease progression, were similar to what was previously seen in the FLAURA trial for the PBS listing of osimertinib for the first-line treatment of *EGFRm* NSCLC. Within FLAURA, a large proportion of patients continued treatment beyond progression (67% and 70% in osimertinib and standard care arms for a median of 8 and 7 weeks, respectively) (para 6.10, osimertinib PSD, July 2020 PBAC meeting). For the PBS listing of osimertinib, the ESC concluded that even though treatment continuation with osimertinib after disease progression was of reasonable concern, it was unlikely to have had a significant impact on the OS benefit of first-line osimertinib (para 6.11, osimertinib PSD, July 2020 PBAC meeting).
- 6.19 The KM plot for OS initially showed there were more deaths in the O+C arm than the osimertinib arm, with the curves crossing at approximately 16 months suggesting that the proportional hazards assumption for OS had been violated (Figure 2). The submission reported that prior to the curve separation, in the O+C arm, there was no notable clustering of adverse events (AEs) resulting in a fatal outcome that would highlight a potential higher risk of death in this population. No further analysis on those that died in the first 16 months was presented by the submission. The submission did not acknowledge the violation of the proportional hazards assumption for OS, and did not present alternative methods of evaluating OS, such as restricted mean survival time. The HR, CIs and p-values for this analysis should be interpreted with caution. The PSCR stated the OS data showed a strong numeric trend favouring O+C (HR 0.75 (95% CI 0.57, 0.97) although the p-value did not reach the required value for statistical significance of ≤ 0.000001 . The sponsor further stated that as the OS data are approaching maturity, there is unlikely to be a substantial change in the trend demonstrated in the DCO2 results.
- 6.20 The PSCR acknowledged that the crossing of the KM curve at month 16 represented a violation of the constant proportional hazard assumption in the KM analysis, however argued that the effect was very small. The ESC disagreed with the PSCR's interpretation and advised that the toxicity of each component of therapy requires careful consideration when combining treatment options with known significant toxicity.

Exploratory outcome (time to treatment discontinuation (TTD))

- 6.21 The Kaplan-Meier curves for time to treatment discontinuation (TTD) and PFS for O+C and osimertinib are in Figure 3.
- 6.22 TTD was used to inform treatment use in the economic model. The comparison provided was only partially informative as the submission modelled osimertinib and chemotherapy TTD curves separately in the O+C arm for the economic model.

6.23 The submission reported that the TTD data from FLAURA2 was relatively mature, with 44.1% and 54.3% of TTD events for osimertinib occurring in the O+C and osimertinib arms, respectively. For pemetrexed in the O+C arm, 74.9% of TTD events had occurred. Based on the comparison of PFS and TTD KM curves, it was apparent that more patients in the osimertinib arm continued treatment post-progression when compared to patients in the O+C arm.

Figure 3: Post-hoc comparison of PFS and TTD KM data (DCO1: 3 April 2023)



Source: Figure 2.13, p 87 of the submission
 KM = Kaplan Meier; Osimertinib = osimertinib; O+C = osimertinib plus chemotherapy; PFS = progression-free survival; TTD = time to treatment discontinuation.

Exploratory outcome (HRQoL, EQ-5D-5L)

6.24 EQ-5D-5L results were reported as an exploratory endpoint in FLAURA2 at DCO1. Australian tariffs were used to estimate utility values in the economic model. The submission reported that both treatment arms were well balanced in terms of mean EQ-5D-5L visual analogue scale (VAS) score at baseline (71.7 in the O+C arm and 70.6 in the osimertinib arm). Post-baseline, mean EQ-5D-5L VAS scores increased showing an improvement across both treatment arms, with no notable differences between arms. The submission did not present a summary table of EQ-5D-5L data, nor did it present any analysis to show the mean differences between timepoints throughout the trial. The ESC noted QoL is an important treatment goal for patients with advanced disease and reflected on the increased AEs reported with O+C compared to osimertinib monotherapy.

Comparative harms

- 6.25 A summary of the safety data from FLAURA2 is presented in Table 6. The safety analysis set consisted of all subjects within the study who received at least one dose of study treatment. The period of observation for adverse events (DCO 1) was shorter than the period of observation for the benefits described at DCO2.
- 6.26 Treatment with O+C was associated with a higher frequency of Grade 3 or above treatment emergent adverse events (TEAEs) when compared to osimertinib (63.8% vs. 27.3%). Serious adverse events (SAEs) were reported more frequently for O+C (37.7%) than for osimertinib (19.3%).
- 6.27 When reviewing Common Terminology Criteria for Adverse Events (CTCAE) \geq Grade 3 adverse events (AE) the following observations were made:
- the most frequently reported CTCAE \geq Grade 3 AEs in the O+C treatment arm were anaemia (19.9%), neutropenia (13.4%) and decreased neutrophil count (11.2%). The submission claimed that this reflected the known haematological toxicity profile of the individual chemotherapy components.
 - the most frequently reported CTCAE \geq Grade 3 AEs in the osimertinib treatment arm were pneumonia (1.8%), COVID-19 pneumonia (1.8%), hypertension (1.5%) and interstitial lung disease (1.5%). These AEs were consistent with the known osimertinib safety profile.
- The O+C arm was associated with a higher rate of AEs than the osimertinib arm across the majority of reported AE's by System Organ Class and Preferred Term recorded.
- 6.28 The pattern of AEs reported in both treatment arms of FLAURA2 was as expected for NSCLC patients receiving EGFR-TKIs and cisplatin/ carboplatin and pemetrexed chemotherapy in the first-line setting. No new safety signals were identified. However, the frequency of some of the observed AEs appeared to be higher than what is typically seen with the individual components of the O+C arm, potentially suggesting a synergistic relationship in relation to toxicity. For example, the number of reported AEs described as causally related to osimertinib was higher in the O+C arm than the osimertinib arm (29.3% vs 10.5%). Additionally, pemetrexed was thought to be causally related to 47.1% of the noted \geq Grade 3 treatment related AE in the O+C arm. This may reflect a longer duration of exposure to pemetrexed compared to what is typically seen in similar patient populations, combined with the idea that prolonged treatment with maintenance pemetrexed has been noted to result in cumulative toxicities¹⁰.
- 6.29 A higher proportion of patients in the O+C arm had AEs leading to discontinuation of any study drug (47.8%) compared to the osimertinib arm (6.2%), mainly due to

¹⁰ Faber, M. G., Wang, C., Reddy, S. K., Meagher, A., Early, A., Chen, H., & Dy, G. K. (2022). Survival outcomes of alternate dosing schedule of pemetrexed as maintenance therapy in NSCLC: Single institution experience. *Lung Cancer*, 165, 49–53. <https://doi.org/10.1016/j.lungcan.2022.01.010>

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discontinuation of chemotherapy in 125 patients (45.3%). AEs leading to discontinuation of carboplatin/cisplatin were reported in 46 patients (16.7%), and AEs leading to discontinuation of pemetrexed were reported in 119 patients (43.1%). The submission reported that when given concurrently with chemotherapy, osimertinib was well tolerated, with 30 patients (10.9%) in the O+C arm reporting any AE leading to osimertinib discontinuation compared with 17 patients (6.2%) in the osimertinib arm. The difference in discontinuation between the two treatment arms associated with osimertinib was higher in the O+C arm which may be suggestive of a synergistic relationship in relation to toxicity.

- 6.30 The PSCR disputed there may be a synergistic relationship between the components of the combination therapy when compared with osimertinib monotherapy. The ESC noted that osimertinib TEAE; TEAE leading to treatment discontinuation; and TEAE leading to death were higher in the O+C arm than the osimertinib monotherapy arm.

Table 6: Summary of AEs (Safety Analysis Set; DCO: 3 April 2023)

AE category	O+C (N= 276)	Osimertinib (N= 275)	RR (95% CI) ^a
Any AE	276 (100)	268 (97.5)	1.03 (1.01, 1.05)
Any treatment related AE	269 (97.5)	241 (87.6)	1.11 (1.06, 1.17)
Any SAEs (including events with the outcome of death)	104 (37.7)	53 (19.3)	1.96 (1.47, 2.60)
Any treatment related SAE	52 (18.8)	15 (5.5)	3.45 (1.99, 5.98)
CTCAE ≥ Grade 3 AEs	176 (63.8)	75 (27.3)	2.34 (1.89, 2.89)
Any CTCAE ≥ Grade 3 treatment related AEs	146 (52.9)	29 (10.5)	5.02 (3.49, 7.20)
Any AE leading to treatment discontinuation	132 (47.8)	17 (6.2)	7.74 (4.80, 12.46)
Any treatment related AE leading to discontinuation	30 (10.9)	17 (6.2)	1.76 (0.99, 3.11)
Any AE resulting in death	18 (6.5)	8 (2.9)	2.24 (0.99, 5.07)
Any treatment related AE resulting in death	5 (1.8)	1 (0.4)	4.98 (0.59, 42.37)
Select CTCAE ≥ Grade 3 AE (MedDRA PT; > 5% incidence in either arm)			
Anaemia	55 (19.9)	1 (0.4)	54.80 (7.64, 393.22)
Neutropenia	37 (13.4)	2 (0.7)	18.43 (4.49, 75.73)
Neutrophil count decreased	31 (11.2)	2 (0.7)	15.44 (3.73, 63.90)
Platelet count decreased	21 (7.6)	0	0
Thrombocytopenia	19 (6.9)	3 (1.1)	6.31 (1.89, 21.08)
Febrile neutropenia	11 (4.0)	0	0
Select AE any grade (MedDRA PT)			
Anaemia	128 (46.4)	22 (8.0)	5.80 (3.81, 8.83)
Diarrhoea	120 (43.5)	112 (40.7)	1.07 (0.88, 1.30)
Nausea	119 (43.1)	28 (10.2)	4.23 (2.91, 6.17)
Rash	77 (27.9)	57 (20.7)	1.35 (1.00, 1.82)
Stomatitis	68 (24.6)	50 (18.2)	1.36 (0.98, 1.87)
Paronychia	65 (23.6)	73 (26.5)	0.89 (0.66, 1.19)

Source: Table 36, pp87 – 88 of the submission, Table 48, pp151 – 152 of Attachment 2.2 of the submission.

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; DCO = data cut off; MedDRA PT = medical dictionary for regulatory activities preferred terms; N = number of patients; O+C = osimertinib plus chemotherapy; SAE = serious adverse event.

^a This analysis was not powered to detect statistical differences in the occurrence of safety events; apparent differences shown in relative measures of effect are exploratory only.

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Benefits/harms

6.31 A summary of benefits and harms for O+C versus osimertinib is presented Table 7.

Table 7: Summary of comparative benefits and harms for O+C and osimertinib

Benefits						
Progression free survival						
April 2023 DCO						
Event	O+C	Osimertinib	Absolute Difference	HR (95% CI)		
Progressed, n/N (%)	120/279 (43.0)	166/278(59.7)	-	0.62 (0.49,0.79) p-value = <0.0001		
Median PFS, months (95% CI)	25.5 (24.7, NC)	16.7 (14.1, 21.3)	8.8			
% not progressed at 12 months (95% CI)	79.7 (74.3, 84.1)	65.5 (59.5, 70.8)	14.2			
% not progressed at 24 months (95% CI)	57.2 (50.4, 63.3)	40.8 (34.7, 46.9)	16.4			
Overall survival						
Event	O+C n/N (%)	Osimertinib n/N (%)	Absolute Difference	HR (95% CI)		
January 2024 DCO						
Deaths, n/N (%)	100/279 (35.8)	126/278 (45.3)		0.75 (0.57, 0.97) p-value = 0.0280		
Median OS, months (95% CI)	NC (38, NC)	36.7 (33.2, NC)	NE			
6-month event-free rate (95% CI)	93.5 (89.9, 95.9)	94.9 (91.6, 97.0)	-1.4			
% Alive at 12-month (95% CI)	88.8 (84.4, 92.0)	92.0 (88.1, 94.7)	-3.2			
% Alive at 18-month (95% CI)	85.5 (80.8, 89.2)	83.9 (79.0, 87.8)	1.6			
% Alive at 24-month (95% CI)	79.7 (74.5, 84.0)	72.1 (66.4, 77.0)	7.6			
Harms						
	O+C n/N	Osimertinib n/N	RR (95% CI) ^a	Event rate/100 patients		RD (95% CI) ^a
				O+C	Osimertinib	
April 2023 DCO						
CTCAE Grade 3 AEs	136/ 276 (49.3)	63/275 (22.9)	2.15 (1.68, 2.76)	49.3	22.9	0.26 (0.18, 0.34)
CTCAE Grade 4 AEs	22 (8.0)	3 (1.1)	7.31 (2.21, 24.13)	7.8	1.1	0.07 (0.03, 0.10)
CTCAE ≥ Grade 3 AEs	176 (63.8)	75 (27.3)	2.34 (1.89, 2.89)	63.8	27.3	0.36 (0.28, 0.45)
Any SAEs (including events with the outcome of death)	104 (37.7)	53 (19.3)	1.96 (1.47, 2.60)	37.7	19.3	0.18 (0.11, 0.26)
Any AE leading to treatment discontinuation	132 (47.8)	17 (6.2)	7.74 (4.80, 12.46)	47.8	6.2	0.42 (0.34, 0.49)
Select TEAEs with severity of Grade ≥ 3						
Anaemia	55 (19.9)	1 (0.4)	54.80 (7.64, 393.22)	19.9	0.4	0.20 (0.15, 0.25)
Neutropenia	37 (13.4)	2 (0.7)	18.43 (4.49, 75.73)	13.4	0.7	0.13 (0.08, 0.17)
Neutrophil count decreased	31 (11.2)	2 (0.7)	15.44 (3.73, 63.90)	11.2	0.7	0.11 (0.06, 0.14)
Platelet count decreased	21 (7.6)	0	0	7.6	0	0.08 (0.04, 0.11)
Thrombocytopenia	19 (6.9)	3 (1.1)	6.31 (1.89, 21.08)	6.9	1.1	0.06 (0.02, 0.09)
Select AE any grade (MedDRA PT)						
Anaemia	128 (46.4)	22 (8.0)	5.80 (3.81, 8.83)	46.4	8.0	0.38 (0.31, 0.46)
Diarrhoea	120 (43.5)	112 (40.7)	1.07 (0.88, 1.30)	43.5	40.7	0.03 (-0.05, 0.11)
Nausea	119 (43.1)	28 (10.2)	4.23 (2.91, 6.17)	43.1	10.2	0.33 (0.26, 0.40)
Rash	77 (27.9)	57 (20.7)	1.35 (1.00, 1.82)	27.9	20.7	0.07 (0.00, 0.14)
Stomatitis	68 (24.6)	50 (18.2)	1.36 (0.98, 1.87)	24.6	18.2	0.06 (0.00, 0.13)
Paronychia	65 (23.6)	73 (26.5)	0.89 (0.66, 1.19)	23.6	26.5	-0.03 (-0.10, 0.04)

Source: Table 18, pp86 – 87 of Attachment 2.2 of the Submission (CSR), Source: Table 25, p 74 of the submission, Table 37, pp 88 – 89

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of the submission, Table 48, pp 151 – 152 of Attachment 2.2 of the submission.

AE = adverse event; CI = confidence interval; CTCAE = Common Terminology Criteria for Adverse Events; HR = hazard ratio; DCO = data cut off; N = number of patients; MedDRA PT = medical dictionary for regulatory activities preferred terms; NC = not calculable; NE = non evaluable; O+C = osimertinib plus chemotherapy; OS = overall survival; RD = risk difference; RR = relative risk; SAE = serious adverse event; TEAE = treatment emergent adverse event.

^a This analysis was not powered to detect statistical differences in the occurrence of safety events; apparent differences shown in relative measures of effect are exploratory only.

6.32 On the basis of direct evidence presented by the submission, for every 100 patients treated with O+C in comparison with osimertinib:

- Approximately 16 more patients would remain progression free at 24 months.
- Approximately 8 more patients would remain alive at 24 months.

6.33 On the basis of direct evidence presented by the submission, for every 100 patients treated with O+C in comparison with osimertinib and followed over a duration of approximately 21 months:

- Approximately 26 more patients would experience an adverse event classified with a severity of CTCAE Grade 3.
- Approximately 7 more patients would experience an adverse event classified with a severity of CTCAE Grade 4.
- Approximately 18 more patients would experience an adverse event classified as serious.
- Approximately 20 more patients would experience Grade 3 or higher anaemia (a condition in which in the blood has reduced ability to carry oxygen).
- Approximately 13 more patients would experience Grade 3 or higher neutropenia (the body has fewer white cells, required to fight infections).
- Approximately 8 more patients would experience Grade 3 or higher platelet (required for the blood to clot) count decrease.
- Approximately 38 more patients would experience anaemia of any grade
- Approximately 33 more patients would experience nausea of any grade
- Approximately 7 more patients would experience rash of any grade

Clinical claim

6.34 The submission claimed that treatment with O+C was superior in efficacy (PFS and OS) compared to osimertinib. The clinical efficacy claim was supported with respect to PFS by a statistically significant and clinically meaningful difference for O+C compared to osimertinib. While the submission reported a difference in OS for O+C compared to osimertinib, it was not statistically significant at the DCO2 analysis. Moreover, the magnitude of the OS benefit was uncertain given the immaturity of the OS data, with the median OS not yet reached for the O+C arm (40.6% events). The ESC agreed the claim of superior PFS may be reasonable but the magnitude of any claimed difference

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for OS was uncertain based on the evidence presented. In particular, the HR should be interpreted with caution given the violation of the proportional hazards assumption. Furthermore, the OS benefit may not be realised in Australian clinical practice given that patients in FLAURA2 could continue treatment beyond progression if clinical benefit was observed.

- 6.35 The submission described O+C as inferior but manageable in terms of safety compared to osimertinib. The ESC agreed the claim of inferior safety was supported, however the claim that the safety profile may be considered 'manageable' was uncertain. Whilst both arms were associated with a high rate of TEAEs, the O+C arm was associated with more frequent Grade ≥ 3 TEAEs and more frequent severe adverse events when compared with osimertinib. The associated management of the severe AEs seen in the O+C arm would likely require an escalation of care. By definition, Grade 3 AEs are medically significant but not immediately life-threatening and may include hospitalisation or prolongation of hospitalisation, be disabling and limit self-care activities of daily living. Grade 4 AEs are acute and life-threatening. The O+C arm when compared to osimertinib was associated with a higher rate of Grade 3 AEs (49.3% vs 22.9%) and also a higher rate of Grade 4 AEs (8.0% vs 1.1%).
- 6.36 The associated safety profiles for both treatment arms are likely to be worse in the real-world clinical setting with patients experiencing less frequent and intensive monitoring versus what was seen in FLAURA2. In addition, the AEs described by the submission were in a healthier population compared to the proposed PBS population (i.e. WHO PS 0 = 37% in the trial vs 17% in Australia), which is likely to result in worse safety outcomes in the Australian population. Overall, a large proportion of patients in the O+C arm compared to osimertinib needed to discontinue treatment due to AEs (47.8% vs 6.2%) indicating this combination was not well tolerated by the trial population.
- 6.37 Overall, the ESC considered that the observed toxicity associated with O+C was an important clinical issue. Given that patients in real-world clinical practice may have poorer baseline health compared to the trial population, the incidence and severity of adverse events may be higher. This may lead to increased rates of treatment discontinuation and mortality, and ultimately reduced therapeutic effect.
- 6.38 The PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.39 The PBAC considered that the claim of inferior comparative safety was reasonable.

Economic analysis

- 6.40 The submission presented a stepped cost-effectiveness and cost-utility analysis, based on the direct randomised trial, FLAURA2. The economic evaluation compared O+C with osimertinib for the first-line treatment of locally advanced/metastatic *EGFRm* NSCLC. Key components of the economic evaluation are presented in Table 8. While a cost-utility analysis was appropriate given the claim of superior effectiveness, it relied

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on the difference observed in the clinical data for PFS, noting that the evidence presented in the submission did not show a statistically significant difference in either OS or quality of life.

Table 8: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	O+C vs osimertinib
Time horizon	10 years in the model base case versus median follow-up in FLAURA2 study of 19.4 months (O+C) and 14.6 months (osimertinib) in PFS (first interim analysis, April 2023) and median follow-up 31.7 months (O+C) and 30.5 months (osimertinib) in OS (second interim analysis, January 2024). The extrapolations of PFS, OS and TTD were carried out over a 15-year period and the analysis was then truncated at 10 years.
Outcomes	Progression-free years gained, life-years gained, quality-adjusted life years gained
Methods used to generate results	Partitioned survival model
Health states	Progression free (PF), progressive disease (PD), death
Cycle length	Monthly (30 days)
Extrapolation method	Point of extrapolation of PFS (from 25 months) and OS (from 37 months) was based on the time when 20% of patients remained at risk, and using parametric functions fitted directly to data from FLAURA2. Australian lifetables applied after end of trial follow-up to capture all-cause mortality observed after the trial. PFS data were based on DCO1 data cut-off (3 April 2023) and OS data were based on DCO2 data cut off (8 January 2024). In the base case, FLAURA2 outcomes (PFS, OS, TTD) were extrapolated based on a Weibull parametric function. For PFS and TTD, the lowest AIC was observed with Gompertz (O+C); and log-logistic (osimertinib). For OS, the lowest AIC was observed with Gompertz. The OS in the O+C arm was assumed to be the same as in the osimertinib arm until 16 months. This was not appropriate given the KM data show OS for O+C was lower up to month 16 than it was for osimertinib. Thereafter, OS in O+C was estimated by applying the trial-based HR for OS to the extrapolated data for the osimertinib arm to generate the rate of death in the O+C arm. No separate extrapolations were applied to OS for O+C.
Health related quality of life	FLAURA2 study EQ-5D-5L using Australian algorithm Viney (2011). PF utility value: 0.814 PD utility value: 0.658 Disutility associated with AEs (applied a one-off QALY adjustment).
Cost of osimertinib	The submission assumed that the cost for osimertinib would be capped to a fixed duration of time, an average of [redacted] months in the O+C arm and an average of [redacted] months in the osimertinib arm (based on current Deed for osimertinib based on FLAURA) based on the submission's proposed risk sharing arrangement (capping the cost to Government for treatment). See paragraph 6.44.

Source: Table 44, pp104-105, Table 56, p132, Table 61, p135, of the submission; Table 18 of the Attachment 2_2 d5169c00001 CSR randomized-period; and page 11 in Valdiviezo (2024).

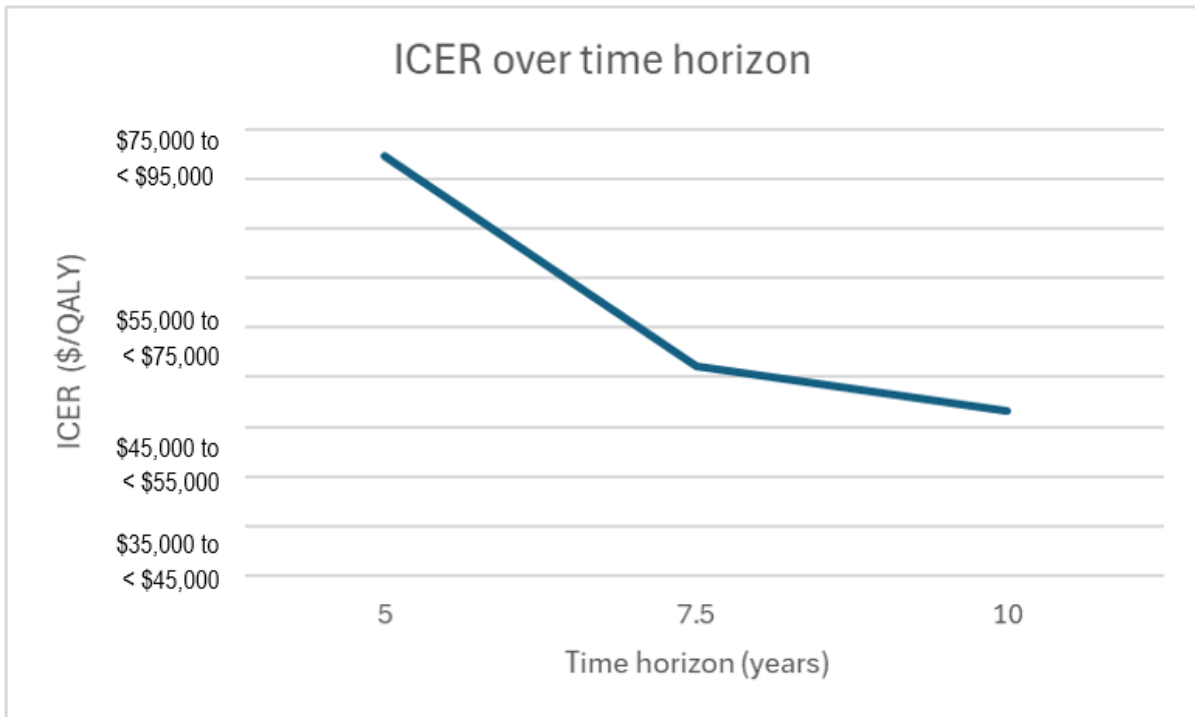
AEs = adverse events; AIC = Akaike Information Criteria; DCO = data cut-off; EQ-5D-5L = EuroQoL, 5 dimensions, 5 level questionnaire, HR = hazard ratio; O+C = osimertinib + chemotherapy; OS = overall survival; PD = progressed disease PF= progression free; PFS = progression free survival; QALY = quality adjusted life years; TTD = time to treatments discontinuation.

6.41 The base case time horizon for 10 years (reported as a truncated analysis from extrapolations over a 15 year period) may not be justified given that the OS data did not demonstrate a statistically significant difference between O+C and osimertinib at the second interim analysis (a p-value of ≤ 0.000001 was required) and at follow-up of

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42 months (3.5 years), 52% of patients in the O+C arm and 46% of patients in the osimertinib arm were alive. On that basis, a 7.5 year time horizon, as per the osimertinib monotherapy submission, may be more reasonable (PSD, July 2019 and July 2020 PBAC meeting). The impact on the incremental cost effectiveness ratio (ICER) of changing the modelled time horizon is presented in Figure 4. The ESC considered a more appropriate time horizon was 7.5 years given the uncertainty associated with immature OS data, and noted this equated to the time horizon used for osimertinib monotherapy. The shorter time period would help mitigate uncertainty associated with the non-significant OS difference in the pivotal evidence. The Pre-PBAC response stated the sponsor maintains a 10-year time horizon is appropriate for several reasons. This includes i) the mean baseline age in FLAURA2 was 60.8 years (which was two years younger than the baseline age in FLAURA at 63.0 years); ii) In the FLAURA2 trial DC02 OS data, 52% and 46% of patients in the OSI + CHEMO and OSI arms, respectively, remained alive at the end of trial follow-up at 42 months; iii) the availability of reasonably effective subsequent therapies and iv) precedents established in PBAC recommendations since 2021.

Figure 4. ICER changes over modelled time horizon (years)



Source: Chart was created based on data from Table 80, p149, Table 82, p 152 and using Economic Evaluation Excel model workbook, data from sheets 'ICER' and 'Input assumptions.'
 ICER=incremental cost-effectiveness ratio; QALY = quality adjusted life years.

6.42 The base case extrapolation function chosen for PFS and OS was Weibull, which was not the best fit (did not have the lowest AIC). For PFS (O+C) Gompertz was the best fit and log-logistic was for the osimertinib arm. The submission claimed that Weibull was used so the PFS arms did not overlap. For OS Gompertz was the best fit, the Weibull was used so that the OS curves did not drop below the PFS curves (the economic

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model adjusted the OS curves so that the O+C arm does not drop below osimertinib). The use of the Weibull in the base case likely overestimated the long term PFS and OS in the O+C arm. The PSCR maintained that the use of the Weibull extrapolation provided a balanced approach, minimising bias against either treatment arm, and avoiding cross over. However, the ESC agreed with the commentary that the Weibull extrapolation likely overestimated the PFS in the O+C arm, and noted that 10% of patients remained in the progression free state at 66 months. Furthermore, the use of the Weibull model was likely to overestimate OS as it did not capture poorer initial survival in the O+C arm. The ESC noted that utilising the Weibull model, it was estimated that approximately 14% of patients remained alive at 10 years in the O+C arm compared to the use of Gompertz model where approximately 2% of patients remained alive at 7.5 years.

- 6.43 The submission assumed that the rate of death in the O+C arm was not higher than in the osimertinib arm in the first 16 months. This does not reflect the occurrence of events in FLAURA2. The submission extrapolated the OS data from the osimertinib arm and then applied the FLAURA2 trial-based HR (HR = 0.75 [95% CI: 0.57, 0.97]; p-value = 0.0280) to the entire duration of the extrapolated OS osimertinib arm to estimate the OS curve of the O+C arm. The O+C KM curve was used in the base case model between months 16 to 37, from which point the extrapolated HR curve was used in O+C arm. The submission stated that although the results were not statistically significant (required p-value of ≤ 0.000001), the PBAC have previously approved superiority claims based on a p-value of 0.05. The evaluation considered this was not appropriate given that statistical significance of OS in FLAURA2 was determined by *a-priori* power calculations within that trial and should not be determined by ex-post considerations. The PSCR stated that the base case economic evaluation assumed the same rate of death in both arms prior to month 16 because of the observed OS curves crossing. The PSCR noted that a sensitivity analysis where the trial-based KM data was used, resulted in a small change to the ICER (increased to \$55,000 to < \$75,000/QALY from \$55,000 to < \$75,000/QALY in the base case). The ESC noted this appeared to have a relatively small effect on the ICER, but did not consider the approach was reasonable given the death rate in the O+C arm was higher than osimertinib monotherapy prior to 16 months (at which point the OS curves crossed). The Pre-PBAC response stated the sponsor base case assumed the same rate of rate of death in both arms prior to month 16. The sponsor would accept the use of the trial-based KM data which resulted in a small change to the ICER.
- 6.44 The submission assumed that the drug cost for osimertinib would be capped to a fixed duration of time, corresponding to an average of [REDACTED] months in the O+C arm and [REDACTED] months in the osimertinib arm, stating this was based on agreed assumptions as part of the monotherapy first line NSCLC listing (1 January 2021) and reflected in the current Deed of Agreement for osimertinib (based on FLAURA). The submission stated that they applied a limitation to the extrapolated TTD to achieve a mean duration in O+C which resulted in an ICER which was consistent with that in the osimertinib

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monotherapy setting (i.e., < \$55,000 to < \$75,000 per QALY gained). On that basis, the use of the resulting [REDACTED] months cap for osimertinib in O+C can be considered as arbitrary (in that it was the duration required to achieve the target ICER; a different target ICER would have resulted in a different cap). Based on FLAURA2 TTD estimates, the mean treatment duration for O+C was 40.6 months, and 28.9 months for osimertinib. The assumption that reimbursement would be capped at [REDACTED] months represents [REDACTED]% of the mean treatment duration (40.6 months) estimated for O+C in the model on the basis of TTD and underestimates the incremental cost of O+C in the model. The terms of a future Deed of Agreement are unknown at this time, and it is not appropriate to assume acceptance of the proposal to cap osimertinib costs to [REDACTED] months when used as part of O+C. The PSCR argued by estimating treatment cost based on a fixed duration, the ICER would remain within the range previously accepted by the PBAC in this setting. However, ESC considered this approach adds complexity and uncertainty.

- 6.45 Health care resource costs associated with management of AEs are summarised in Table 9. The submission assumed that 10% of Grade 3/4 AEs result in hospitalisation, leading to a weighted average cost of AEs of \$216.12 for O+C and \$12.29 for OSI. The ESC noted that the costs associated with treating adverse events appeared substantially underestimated given the toxicity observed with O+C in the FLAURA2 trial. The ESC noted a sensitivity analysis that assumed 50% of patients with grade 3/4 adverse events were hospitalised for both treatment groups (interpreted as half of grade 3 and 4 events in either arm would be treated in hospital), had a relatively minor impact on the ICER (Table 12).

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Table 9: Healthcare resource utilisation and its associated cost associated with treating adverse events

Type of resource item	Unit cost	Source of unit cost	Usage for the proposed medicine	Usage for the comparator
Management of 1L adverse events	O+C arm: \$216.12 Osimertinib arm: \$12.29 Anaemia, Neutropenia, Neutrophil count decreased, Platelet count, decreased and Thrombocytopenia.	Based on incidence of ≥Grade 3 AEs occurring in > 5% of patients in FLAURA2. Costs were based on unit costs of DRG. Based on assumption of 10% of patients requiring hospitalisation (as per advice of 2 clinicians).	Applied as one-off cost in the first cycle of the model	Applied as one-off cost in the first cycle of the model
Management of 2L adverse events	\$86.08 Included: Anaemia, Neutropenia, and Neutrophil count decreased.	Based on incidence reported in chemotherapy arm of AURA3 trial ^a	Applied as a one-off cost to patients commencing post-progression treatment in the PD health state	Applied as a one-off cost to patients commencing post-progression treatment in the PD health state

Source: Table 3.6.1 of the commentary.

a A Phase III, Open-label, Randomized Study of osimertinib versus platinum-based doublet chemotherapy for patients with Locally Advanced or Metastatic Non-small Cell Lung Cancer whose Disease has Progressed with Previous Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Therapy and whose Tumours Harbour a T790M mutation within the Epidermal Growth Factor Receptor Gene.

AEs = adverse events; AR-DRG = Australian Refined Diagnosis Related Group; NSCLC = Non-Small Cell Lung Cancer; O+C = osimertinib + chemotherapy; PD = progressed disease.

6.46 A summary of the key drivers of the model is presented in Table 10.

Table 10: Key drivers of the model

Description	Method/Value	Impact
		Base case: \$ ██████ ¹ /QALY gained
Extrapolation function	OS used Weibull in base case	High, favours O+C Use of Gompertz (in both arms) increased the ICER to \$ ██████ ¹ /QALY gained.
Extrapolation	Using HR approach for O+C OS arm	High, favours osimertinib Use of independent parametric functions (with the lowest AIC) instead of the HR for each arm increased the ICER to \$ ██████ ¹ /QALY gained.
Time horizon	Submission applied time horizon of 10 years	Moderate, favours O+C Use of 7.5 years increased the ICER to \$ ██████ ¹ /QALY gained.

Source: Computed during evaluation.

AIC = Akaike information criterion; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; O+C = osimertinib + chemotherapy; OS = overall survival; QALY = quality adjusted life years.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

6.47 A summary of the results of the stepped economic analysis is presented in Table 11. The results of the submission base case assume drug costs based on a mean duration of funded treatment of ██████ months in the O+C arm, and ██████ months in the osimertinib arm and are based on the proposed effective price.

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Table 11: Results of the stepped economic evaluation

Data	Costs			Health outcomes			ICER
	O+C	Osimertinib	Incremental	O+C	Osimertinib	Increment	
Step 1: FLAURA2 trial based. Outcomes: PFS years gained Cost: osimertinib, chemotherapy and AEs Time horizon: 30 months	\$█	\$█	\$█	1.85	1.53 PFS years gained	0.31 PFS years gained	\$█ ¹ per PFS year gained
Step 2: Time horizon: 10 years Trial data extrapolated Costs: including monitoring, subsequent chemotherapy and end of life care Outcome: LY gained	\$█	\$█	\$█	3.70	3.19 per LY gained	0.506 per LY gained	\$█ ² per LY gained
Step 3: Outcome: QALYs	\$█	\$█	\$█	2.818	2.390 per QALY gained	0.428 per QALY gained	\$█ ³ per QALY gained

Source: Table 78, p149, table 79, p149, Table 80, p150 of the submission.

AE = adverse events; ICER = incremental cost-effectiveness ratio; LY = life years; O+C = osimertinib+ chemotherapy; PFS = progression-free survival; QALY = quality adjusted life years.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$45,000 to < \$55,000

³ \$55,000 to < \$75,000

6.48 The results of key univariate and multivariate sensitivity analyses are summarised in Table 12. During the evaluation additional univariate (parametric functions) and multivariate analyses were conducted. The multivariate sensitivity analyses assumed the use of the lowest parametric function with the lowest AIC/BIC for each outcome (PFS, OS and TTD), use of an extrapolation function (instead of HR approach) for O+C OS, and removing the restriction that the OS O+C curve not be lower than osimertinib.

6.49 The results of these analysis show that the ICER was most sensitive to variations in:

- Choice of modelling of OS curve (using the HR approach or parametric curve approach). Sensitivity analyses in the submission showed that using the parametric function approach, instead of the HR approach, lowered the ICER from \$55,000 to < \$75,000/QALY gained to \$25,000 to < \$35,000. This result is only achieved if the Weibull function is used in the base case, where approximately 14% of patients are alive at 10 years. The use of the Gompertz (with the lowest AIC/BIC) for OS for O+C results in an ICER of \$45,000 to < \$55,000/QALY gained, with approximately 5% of patient in O+C arm alive at 7 years.
- Choice of the parametric function for main outcomes; the submission stated that the Gompertz should not be used for PFS due to the O+C and osimertinib curves crossing. However, the model restricts the O+C curve from being lower than osimertinib, and in the case of the Gompertz, the O+C PFS curve is aligned with osimertinib (log-logistic) PFS after 36 months. When applying the Gompertz for PFS for O+C, the ICER increases marginally to \$55,000 to < \$75,000/QALY gained.

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When the Gompertz is applied to OS, the ICER increases to \$55,000 to < \$75,000/QALY gained. The ESC noted that the use of the curves with the best fit statistics (across all outcomes) increased the ICER to \$55,000 to < \$75,000/QALY gained (lowest AIC analysis). The ESC noted that when the TTD with the lowest AIC is applied, it results in a shorter mean time on treatment (33 months) than occurred with the unrestricted TTD curve applied within the submission’s base case (a mean of 40.6 months).

- The cap on duration of reimbursed osimertinib (drug cost). The removal of the cap proposed for the duration of reimbursed treatment with osimertinib in both arms increased the ICER to \$75,000 to < \$95,000/QALY gained, while removing the cap on the O+C arm costs but not the comparator arm increased the ICER to \$135,000 to < \$155,000/QALY gained.

6.50 The ESC advised that adjustments were required to the economic model. The ESC advised that an appropriate re-specified base case would apply the following: 1) time horizon of 7.5 years; 2) use of extrapolation functions with lowest AIC values; 3) apply adjustment to AE costs. These have been presented in additional multivariate analyses in Table 12. A further analysis is shown in which the proposed cap (scripts) has been removed for the proposed listing, which resulted in a substantially higher ICER.

Table 12: Sensitivity analyses

Base case value	Value used in sensitivity analysis	Incremental cost	Incremental QALY	ICER	% change in ICER
Base Case	-	\$█	0.428	\$█ ¹	-
Time horizon: 10 years	7.5 years	\$█	0.381	\$█ ¹	█%
Truncation point: Based on 20% remaining in risk set (25 months for PFS, 37 months for OS)	Median follow-up (24 months for PFS/TTD and 30 months for OS)	\$█	0.431	\$█ ¹	█%
PFS: Weibull	PFS: Lowest AIC. Gompertz (O+C), Log-logistic (osimertinib)	\$█	0.411	\$█ ¹	█%
OS: Weibull	OS: Gompertz	\$█	0.342	\$█ ¹	█%
OS HR approach	Trial-based KM first 37 months	\$█	0.412	\$█ ¹	█%
Duration of reimbursed osimertinib restriction					
Duration of reimbursed osimertinib. O+C: █ mths Osimertinib: █ mths	O+C: 40.6 mths; Osimertinib: 28.9 mths	\$█	0.428	\$█ ²	█%
O+C: mean duration █ months Osimertinib: mean duration █ months (Deed FLAURA)	O+C: mean duration 40.6 months Osimertinib: mean duration █ months (Deed FLAURA)	\$█	0.428	\$█ ³	█%
10% of Grade3/4 AE's in O+C arm and osimertinib monotherapy that requires hospitalisation. AE costs of \$216.12 for O+C and \$12.29 for osimertinib monotherapy	50% of Grade 3/4 AEs in O+C arm and osimertinib monotherapy that require hospitalisation. AE cost of \$1,080.61 ^a for O+C and \$61.45 for osimertinib monotherapy	\$█	0.428	\$█ ¹	█%

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Base case value	Value used in sensitivity analysis	Incremental cost	Incremental QALY	ICER	% change in ICER
Multivariate analyses					
OS HR approach OS: Weibull	OS independent parametric extrapolation, OS: Gompertz	\$█	0.501	\$█ ⁴	-█%
OS HR approach. PFS, OS, TTD: Weibull.	OS independent parametric extrapolation. PFS, OS, TTD: lowest AIC ^a	\$█	0.353	\$█ ¹	█%
OS HR approach, OS: Weibull	Trial-based KM first 37 months ^c OS: Gompertz	\$█	0.327	\$█ ¹	█%
PFS, OS, TTD: Weibull. Time horizon 10 years	PFS, OS, TTD: lowest AIC ^b . Time horizon: 7.5 years	\$█	0.330	\$█ ¹	█%
PFS, OS, TTD: Weibull. Time horizon 10 years AE costs of \$216.12 for O+C and \$12.29 for osimertinib monotherapy	PFS, OS, TTD: lowest AIC ^a . Time horizon: 7.5 years AE costs of \$1,080.61 ^a for O+C and \$61,45 cap for osimertinib monotherapy	\$█	0.330	\$█ ¹	█%
PFS, OS, TTD: Weibull. Time horizon 10 years AE costs of \$216.12 for O+C and \$12.29 for osimertinib monotherapy. O+C: mean duration █ months Osimertinib monotherapy: mean duration █ months (Deed FLAURA)	PFS, OS, TTD: lowest AIC ^b . Time horizon: 7.5 years AE costs of \$1,080.61 ^a for O+C and \$61,45 for osimertinib monotherapy O+C mean duration: 33 months ^d Osimertinib monotherapy: mean duration █ months (Deed FLAURA)	\$█	0.330	\$█ ⁵	█%

Source: Table 62, p136, Table 81, pp150-151, Table 82, p152 of the submission.

Values in italics were calculated during evaluation.

AIC = Akaike Information Criterion; DoT = duration of treatment; HR = hazard ratio; ICER = incremental cost-effectiveness ratio; KM = Kaplan Meier; OS = overall survival; PFS = progression-free survival; QALY = quality adjusted life years; TTD = time to treatment discontinuation.

^a Adjusted Excel Economic Model in sheet 'Cost of 1L AE' in cells Cell B22 from formula and inserted '50%'.

^b Lowest AIC PFS: Gompertz (O+C), Log-logistic (osimertinib), OS: Gompertz (O+C), Gompertz (osimertinib), TTD: Gompertz (O+C), Log-logistic (osimertinib). Log-normal (pemetrexed).

^c The submission included assumptions that OS (O+C) cannot be lower than OS (osimertinib), OS cannot be lower than PFS and PFS (O+C) cannot be lower than PFS (osimertinib).

^d Unrestricted TTD in O+C arm: adjusted Excel Economic Model in sheet 'Input Assumptions' in cells L36 to 180 (months) (full extrapolation to 15 years).

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$135,000 to < \$155,000

⁴ \$45,000 to < \$55,000

⁵ \$115,000 to < \$135,000

O+C cost/ course

6.51 The average cost of treatment of osimertinib (O+C) per patient per course of treatment was estimated by the economic model to be \$█ (discounted), and for osimertinib (monotherapy) the cost was estimated to be \$█ (discounted). The costs were based on the assumed capped reimbursed duration of treatment of █ months in O+C arm and a current agreed cap of reimbursed duration of treatment of █ months for osimertinib. The submission assumed a 100% relative dose intensity in the model.

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Table 13: Drug cost per patient for proposed and comparator drugs (applying effective price for osimertinib)

	O+C			Osimertinib		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose	Osimertinib: 80 mg/day Chemotherapy: mean dose not reported; Cisplatin initial dose 75 mg/m ² ; Carboplatin initial dose 750 mg; Pemetrexed initial dose: 500 mg/m ²	Osimertinib: 80 mg/day Chemotherapy: Cisplatin 128 mg; carboplatin 575 mg; Pemetrexed 855 mg	Osimertinib: 80 mg/day Chemotherapy: Cisplatin 128 mg; carboplatin 575 mg; Pemetrexed 855 mg	80 mg/day	80 mg/day	80 mg/day
Mean duration/exposure	Osimertinib (30 day cycle): 19.67 months Chemotherapy (21-day cycle): cisplatin/carboplatin 3.5 infusions / 2.58 months Pemetrexed: 16.5 infusions / 12.06 months	Osimertinib (30 day cycle): [redacted] months Chemotherapy (21-day cycle): cisplatin/carboplatin 3.5 infusions Pemetrexed: 17 months / 24.6 infusions	Osimertinib: [redacted] months Chemotherapy (21 day cycles): cisplatin/carboplatin: 2.6 months (estimated: 3.74 scripts) Pemetrexed: 17 months (estimated 24 scripts)	18.12 months	[redacted] months	[redacted] months
Cost/patient/month/script	Osimertinib: \$[redacted] Chemotherapy. Cisplatin: \$141.81 /infusion Carboplatin: \$165.44 / infusion Pemetrexed: \$160.02 /infusion	Osimertinib: \$[redacted] per 30 day cycle. Chemotherapy. Cisplatin: \$141.81 /infusion Carboplatin: \$165.44 / infusion Pemetrexed: \$160.02 /infusion	Osimertinib: \$[redacted] per 30 days (month) Chemotherapy ^b (weighted costs) Cisplatin: \$148.49 /script Carboplatin: \$172.17 / script Pemetrexed: \$166.74 /script	\$[redacted]	\$[redacted] per 30 day cycle.	\$[redacted] per script
Cost/patient/course	(= \$[redacted] + \$523 ^a + \$2,640)	(= \$[redacted] + \$523 ^a + \$3,936)	(= \$[redacted] + \$584 + \$4,084)	\$[redacted]	\$[redacted]	\$[redacted]

Source: Calculated and compiled during evaluation.

^a cisplatin/carboplatin cost per course was a weighted average 32.1% carboplatin use and 67.9% cisplatin use.

^b cost of chemotherapy was based on efficient combination of vials.

^c the duration of exposure in the trial was based on 1 month = 30.4375 days, however, for simplicity the duration (months) was rounded to 30 days per months

Estimated PBS usage & financial implications

6.52 This submission was not considered by DUSC.

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6.53 The submission adopted a combined market share (with regard to uptake and use) and epidemiological approach (with regard to patient numbers) to estimate utilisation of O+C and its comparator osimertinib. Details of the key inputs for the financial estimates are presented in Table 14. In relation to estimated utilisation, the ESC considered that the uptake of O+C (█% of patients eligible for first-line osimertinib) was substantially overestimated by the submission, noting the toxicity of O+C and that the NCCN guidelines recommend osimertinib as the preferred treatment over O+C.

Table 14: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Incident patients treated with osimertinib (monotherapy) in 1st line advanced/ metastatic EGFRm NSCLC	█ ¹ in Yr1 to █ ¹ in Yr 6.	
Uptake rate	█%	The PBAC considered the uptake uncertain, noting the toxicity of O+C
Eligible incident patients	█ ² in Yr1 to █ ² in Yr6	
Prevalent patients	█ ² in Yr 1 (assumed informal use with chemotherapy funded by hospitals/patients prior to PBS listing)	Uncertain, the current PBS listing osimertinib (monotherapy) states that the treatment must be the sole PBS-subsidised therapy for this condition, therefore the chemotherapy would need to be accessed via non-PBS funding.
Compliance rate	100%	The assumption may be reasonable; however, compliance rate was not reported in the FLAURA2 study.
Dose/duration	The scripts per patient were estimated based on a proposed capped reimbursement for assumed duration of █ months (O+C) and capped duration of █ months (osimertinib) of treatment based on the current Deed of Agreement 2021	
MBS item	MBS item 13950 (80% rebate) for the infusion of chemotherapy.	Appropriate.

Source: Compiled during evaluation from Section 4 of the submission.

MBS = Medicare Benefits Schedule; EGFRm = epidermal growth factor receptor mutations; NSCLC = non-small cell lung cancer; O+C = osimertinib + chemotherapy; PBS = Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

6.54 The submission assumed that some patients who would have initiated osimertinib monotherapy, would initiate O+C from the time the TGA approval is granted but before the PBS listing is finalised. The submission stated that patients would pay for the chemotherapy portion of O+C out of pocket but would then contribute to the prevalent patient pool with a limited duration of PBS reimbursed treatment.

6.55 A summary of the estimated use and financial implications is presented in Table 15.

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Table 15: Estimated use and financial implications (applying the effective price of osimertinib)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients initiating treatment	■ ^{a1}	■ ²	■ ²	■ ²	■ ²	■ ²
Number of patient years treated	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹	■ ¹
Number of scripts dispensed ^b	■ ³	■ ⁴	■ ³	■ ³	■ ³	■ ³
Estimated financial implications of osimertinib (O+C)						
Cost to PBS/RPBS less copayments	\$■ ⁵	\$■ ⁶	\$■ ⁷	\$■ ⁷	\$■ ⁷	\$■ ⁷
Estimated financial implications for osimertinib (monotherapy) and chemotherapy (cisplatin/carboplatin, pemetrexed)						
Cost to PBS/RPBS less copayments, osimertinib	-\$■ ⁸	-\$■ ⁸	-\$■ ⁸	-\$■ ⁸	-\$■ ⁸	-\$■ ⁸
Cost to PBS/RPBS less copayments, chemotherapy	\$■ ⁹	\$■ ⁹	\$■ ⁹	\$■ ⁹	\$■ ⁹	\$■ ⁹
Cost to PBS/RPBS less copayments, total	-\$■ ⁸	-\$■ ⁸	-\$■ ⁸	-\$■ ⁸	-\$■ ⁸	-\$■ ⁸
Net financial implications						
Net cost to PBS/RPBS	\$■ ⁹	\$■ ¹⁰	\$■ ⁹	\$■ ⁹	\$■ ⁹	\$■ ⁹
Net cost to MBS	\$■ ⁹	\$■ ⁹	\$■ ⁹	\$■ ⁹	\$■ ⁹	\$■ ⁹
Net cost to PBS/RPBS/MBS	\$■ ⁹	\$■ ¹⁰	\$■ ⁹	\$■ ⁹	\$■ ⁹	\$■ ⁹

Source: Table 94, p160, Table 100, p163, and Table 119, p174 of the submission.

Values in italics were calculated during evaluation from Table 107, p167 and Table 112 – 114, p171 of the submission.

PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.

^a Includes < 500 prevalent patients

^b Assuming mean ■ months duration of reimbursed treatment per year as estimated by the submission.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ 5,000 to < 10,000

⁴ 10,000 to < 20,000

⁵ \$20 million to < \$30 million

⁶ \$40 million to < \$50 million

⁷ \$30 million to < \$40 million

⁸ net cost saving

⁹ \$0 to < \$10 million

¹⁰ \$10 million to < \$20 million

6.56 The total net cost to the PBS/RPBS of listing osimertinib (O+C) was estimated to be \$0 to < \$10 million in Year 6, and a total of \$40 million to < \$50 million in the first 6 years of listing. The total net cost to the Government for listing O+C was estimated to be \$0 to < \$10 million in Year 6, a total of \$50 million to < \$60 million in the first 6 years of listing.

6.57 The cost is likely overestimated due to the submission assuming that prevalent patients in Year 1 would use O+C before the PBS approved listing. Excluding the prevalent patients would decrease the total net cost to the PBS/RPBS from \$40 million to < \$50 million to \$40 million to < \$50 million in the first 6 years of listing.

6.58 Two additional sensitivity analyses were conducted during the evaluation to estimate the net financial impact of removing the cap on DoT for osimertinib based on the economic model: for O+C from ■ months to 40.6 months, and for osimertinib from

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■■■■ months to 28.9 months. The estimated DoT of 40.6 months was drawn from the FLAURA2 study (TTD data), where patients were allowed to continue treatment after progression. The first sensitivity analysis removed only the O+C cap, with the total net cost to the PBS/RPBS/MBS increased from \$50 million to < \$60 million over the first 6 years of listing to \$100 million to < \$200 million. A sensitivity analysis which removed the duration of treatment cap from the O+C and osimertinib arms increased the net financial impact to \$70 million to < \$80 million.

- 6.59 The submission did not include the cost of pemetrexed treatment for prevalent patients who would commence treatment before PBS listing. Based on 17 months DoT as estimated in the economic model, and adjusting by 6 months (self-funding of pemetrexed), the cost to the Government for the additional 11 months of pemetrexed treatment for the < 500 prevalent patients (= < 500 patient years) would be \$0 to < \$10 million in Year 1 (an additional 5,000 to < 10,000 scripts).

Financial Management – Risk Sharing Arrangements

- 6.60 There is a current Deed of Agreement for osimertinib which includes use in first-line, second-line and adjuvant treatment of *EGFRm* positive NSCLC. For context, osimertinib was PBS-listed on 1 February 2019 for the second-line treatment of stage IIIB or IV *EGFRm* NSCLC. The listing expanded from 1 January 2021 to include the first-line treatment of stage IIIB or IV *EGFRm* NSCLC. A further expansion to the PBS listing of osimertinib occurred on 1 June 2024 to include the treatment of Stage IB, to IIIA NSCLC as adjuvant therapy after surgical resection. Reimbursements above subsidisation caps are agreed at ■■■■%, resulting in no additional Commonwealth expenditure beyond agreed estimates.
- 6.61 The submission stated that the sponsor is willing to enter a risk-sharing arrangement (RSA) related to the proposed listing of O+C on the PBS. The submission proposed expenditure caps for the proposed listing, including a treatment duration of ■■■■ months per patient compared with the osimertinib monotherapy agreed duration of ■■■■ months per patient. The ESC noted the proposal corresponded to an increase of ■■■■% in Government expenditure for osimertinib (calculated based on Table 13).
- 6.62 The submission stated that the expenditure caps in the current osimertinib (monotherapy) Deed of Agreement have been ■■■■ ■■■■ ■■■■ and are expected to be ■■■■ ■■■■ ■■■■ ■■■■ ■■■■. The submission did not present any data regarding the number of patients or duration of treatment of current patients in Australia using osimertinib. The ESC noted that the current expenditure caps for osimertinib include three indications, first-line, second-line and adjuvant treatment. The Pre-PBAC response noted the ■■■■ ■■■■ ■■■■ is a result of all indications in the RSA, noting the current ■■■■ ■■■■ ■■■■ ■■■■ ■■■■ ■■■■ is due to first-line and second-line indications having higher utilisation than agreed.
- 6.63 The DUSC Secretariat provided ESC with an estimate of the average number of prescriptions supplied per patient for the period 1 January 2021 (correlating with the

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improvement in progression free survival (PFS) but overall survival (OS) data were immature and it was associated with increased toxicity. The PBAC considered the economic model was based on optimistic assumptions and overestimated the benefit of O+C. The PBAC considered the uptake rate of O+C in the submission to be substantially overestimated given the safety profile of the treatment. The PBAC considered the outstanding issues could be addressed in an early re-entry submission.

- 7.2 The PBAC considered the primary reason for this outcome was due to the economic analysis provided in the submission.
- 7.3 The PBAC noted that there is a moderate clinical need for more effective therapies for metastatic *EGFR*^m NSCLC, given that there is poor survival for patients and currently PBS-listed therapies are only moderately effective. The PBAC acknowledged the unmet clinical need described in the Consumer Comments from organisations and individuals supporting an additional treatment option to treat *EGFR*^m NSCLC. The PBAC further noted the Thoracic Oncology Group of Australasia stated not all patients will be fit enough nor accepting of having the combination of O+C.
- 7.4 The PBAC noted osimertinib with or without chemotherapy was recommended for the first line treatment of patients with exon 19 deletions or exon 21 L858R substitution mutations, and osimertinib monotherapy was the preferred option given the need to balance efficacy with toxicity in some treatment guidelines including those published by the National Comprehensive Cancer Network (Version 3, 2025¹¹) and the American Society of Clinical Oncology (Owen JCO 2025¹²).
- 7.5 The PBAC noted the following with regards to the restriction criteria proposed in the submission for use in combination with chemotherapy:
- the 40 mg strength should be listed for continuing treatment only;
 - the number of repeats for the initial restriction should be reduced from 5 to 2;
 - the criteria should specify an WHO performance status of 1 or less, consistent with the FLAURA2 trial and noting the toxicity profile of O+C;
 - it is appropriate to remain silent on the *EGFR* mutation type (similar to osimertinib monotherapy), as use outside the appropriate mutation would be unlikely; and
 - allow the change to the PBS indication to include 'stage IIIB/IIIC (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)' and for this to be flowed on to all PBS listings currently listed for Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC).

¹¹ National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. (Version 3 2025).

¹² Owen DH, Ismaila N, Ahluwalia A, Feldman J, Gadgeel S, Mullane M, Naidoo J, Presley CJ, Reuss JE, Singhi EK, Patel JD. Therapy for Stage IV Non-Small Cell Lung Cancer With Driver Alterations: ASCO Living Guideline, Version 2024.3. J Clin Oncol. 2025 Apr;43(10):e2-e16. doi: 10.1200/JCO-24-02785. Epub 2025 Feb 27. PMID: 40014839.

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- 7.6 With regards to the restriction criteria, the PBAC considered it would be preferable to have a single, combined listing allowing either osimertinib monotherapy or osimertinib in combination with chemotherapy. The PBAC noted this could be achieved by removing the clinical criterion “The treatment must be the sole PBS-subsidised therapy for this condition” from the current listing. This would allow clinician discretion with regards to the nature and duration of concomitant chemotherapy. The PBAC noted that this would require a weighted price for osimertinib in the first-line locally advanced/metastatic setting.
- 7.7 The PBAC considered that the submission’s nomination of osimertinib as the main comparator for the first-line treatment of locally advanced or metastatic *EGFR*m NSCLC was appropriate. The PBAC noted some patients are already able to access subsidised osimertinib in combination with chemotherapy, if the chemotherapy component is funded by either hospitals or patients.
- 7.8 The PBAC noted the clinical evidence for O+C was based on the FLAURA2 trial (n = 557), which was a head-to-head randomised controlled trial comparing the efficacy and safety of O+C to osimertinib as first-line treatment in patients with locally advanced or metastatic *EGFR*m NSCLC (specifically, exon 19 deletion or exon 21 L858R substitution mutations). The PBAC noted there was a statistically significant improvement in PFS for O+C compared to osimertinib with a hazard ratio (HR) of 0.62 ([95% CI: 0.49, 0.79]; p-value < 0.0001) and a median incremental PFS gain of 8.8 months (25.5 months median PFS in the O+C arm compared to 16.7 months median PFS in the osimertinib arm). The PBAC noted the OS data was immature with 40.6% events and a non-statistically significant HR, with a final analysis to be conducted when the OS data is 60% mature (anticipated first half of 2026). The PBAC considered it would be informative to review the OS data when it is available.
- 7.9 The PBAC acknowledged the moderate improvement in PFS, with the improvement being similar to that observed in FLAURA trial of osimertinib monotherapy compared to standard of care. However, the PBAC agreed with the ESC and the evaluation, that the magnitude of the clinical benefit in FLAURA2 was uncertain due to the immaturity of the OS data, and the violation of the proportional hazards assumption for OS initially showing more deaths in the O+C arm than the osimertinib arm with the curves then crossing at approximately 16 months.
- 7.10 The PBAC considered the observed toxicity with O+C was an important clinical issue and noted whilst both arms were associated with a high rate of treatment emergent adverse events (TEAEs) the O+C arm was associated with more frequent Grade \geq 3 TEAEs (O+C 63.8% vs osimertinib 27.3%) and with more severe adverse events when compared with osimertinib (O+C 37.7% vs osimertinib 19.3%). The PBAC agreed with the ESC that quality of life (QoL) is an important treatment goal for patients and considered the claim the safety profile is ‘manageable’ was not informative. Given that patients in real-world clinical practice may have poorer baseline health compared to the trial population, the incidence and severity of adverse events may be higher. This may lead to increased rates of treatment discontinuation and mortality and ultimately

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reduced therapeutic effect. The PBAC also noted the requirement for three weekly infusions of chemotherapy would result in additional time toxicity¹³.

- 7.11 The submission presented a cost utility analysis based on the results of the FLAURA2 trial (median follow up approximately 31 months). The PBAC noted base case economic model resulted in an incremental cost effectiveness ratio of \$55,000 to < \$75,000 per quality adjusted life year gained. The PBAC noted the economic model was sensitive to the approach to extrapolation including the functions applied (see paragraphs 6.42, 6.43, 6.49). The PBAC considered there was low certainty in the modelled benefits and that, overall, the modelled benefit of O+C was overestimated. The PBAC considered applying a time horizon of 10 years further increased the uncertainty in the modelled results. Additionally, the PBAC agreed with the ESC that the costs associated with treating adverse events were overestimated.
- 7.12 The PBAC noted the economic model presented in the submission included a capped treatment duration for O+C of [REDACTED] months and agreed with the ESC that this adds complexity and uncertainty and considered it should be removed from the base case model.
- 7.13 The PBAC considered the ESC respecified base case model (as outlined in paragraph 6.50) with the treatment duration cap for O+C removed provided a reasonable basis for assessing the cost-effectiveness of O+C compared to osimertinib. The PBAC noted the ICER increased from \$55,000 to < \$75,000 per QALY to \$115,000 to < \$135,000 per QALY (based on an average treatment duration of 33 months for O+C).
- 7.14 The PBAC noted the submission used a market share approach to estimate the number of patients that would initiate treatment with O+C each year. The PBAC considered the assumed uptake of O+C of [REDACTED]% of patients eligible for first-line osimertinib monotherapy was overestimated, noting the toxicity of the combination. The PBAC considered the financial estimates would require revision and advised it would be reasonable to consider an uptake rate of 30% to 40%. The PBAC considered the inclusion of some prevalent patients (assumed to be using non-PBS funded chemotherapy at the time of listing of O+C) was appropriate; however, the uptake in this population should be less than 30%. The PBAC noted the financial estimates assumed a capped treatment duration of [REDACTED] months per patient and considered this was not appropriate and the financials should apply a mean treatment duration of 33 months (consistent with the economic model outlined in paragraph 7.13).
- 7.15 The PBAC considered it would be appropriate for O+C to join the risk sharing agreement for osimertinib that currently includes the PBS listings for first-line, second-line, adjuvant use. An increase in the caps to account for additional net expenditure on osimertinib associated with the extended listing would be reasonable.

¹³ Gupta A, Eisenhauer EA and Booth CM. The time toxicity of cancer treatment. *Journal of Clinical Oncology*; 40 (15): 1611-1615

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7.16 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for O+C using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- Propose a single combined listing as outlined in paragraph 7.6;
- Reduce price to give an ICER less than \$55,000 to < \$75,000 per QALY gained using the revised model as outlined in paragraph 7.13;
- Revision of the financial estimates, as outlined in paragraph 7.14
- Propose a revised osimertinib risk-sharing arrangement proposal, as discussed in 7.15

The early re-entry resubmission must be lodged by week 7 of the next two PBAC cycles. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

7.17 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:

Not recommended

8 Context for Decision

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

9 Sponsor's Comment

The sponsor had no comment.