

6.01 ALECTINIB, Capsule 150 mg, Alecensa® ROCHE PRODUCTS PTY LTD

1 Purpose of submission

- 1.1 The Category 2 submission requested the Section 85 Telephone or Online Authority listing of alectinib for adjuvant treatment in adult patients following tumour resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumours ≥ 4 cm or node positive).
- 1.2 Listing was requested on the basis of a cost-effectiveness analysis versus platinum-based chemotherapy. Table 1 summarises the components of the overall clinical claim addressed by the submission.
- 1.3 The PBAC noted that an application was submitted by the sponsor to the MSAC Executive requesting an amendment to MBS item 73341 that would allow FISH testing for ALK in patients with resectable NSCLC.

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

| Component | Description |
|----------------|--|
| Population | Patients with resected ALK-positive NSCLC (tumours ≥ 4 cm or node positive) |
| Intervention | Adjuvant treatment with 600 mg alectinib (4 x 150 mg capsules) administered orally twice daily for a maximum treatment duration of 2 years |
| Comparator | Adjuvant treatment with platinum-based chemotherapy (4 x 21-day cycles) |
| Outcomes | Disease-free survival Overall survival Safety |
| Clinical claim | In patients with resected ALK-positive NSCLC (tumours ≥ 4 cm or node positive), adjuvant treatment with alectinib is more effective in prolonging disease-free survival than platinum-based chemotherapy. Alectinib is superior in effectiveness and similar in safety compared with platinum-based chemotherapy. |

Source: Table 1.1, p3 of the submission.

ALK=anaplastic lymphoma kinase; NSCLC=non-small cell lung cancer.

2 Background

Registration status

- 2.1 Alectinib was registered by the Therapeutic Goods Administration (TGA) on 23 December 2024 for adjuvant treatment in adult patients following tumour resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumours ≥ 4 cm or node positive).

Previous PBAC consideration

- 2.2 The Pharmaceutical Benefits Advisory Committee (PBAC) has not previously considered alectinib for this indication.
- 2.3 Alectinib is currently listed on the Pharmaceutical Benefits Scheme (PBS) for stage IIIB (locally advanced) or stage IV (metastatic) NSCLC.

3 Requested listing

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

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|---|---------------------|----------------------|----------------------|----------------|------------------|
| ALECTINIB | | | | | |
| alectinib 150 mg capsule, 224 4 x 56 | NEW | 1 | 224 | 3 | Alecensa |
| Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) | | | | | |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | | |
| Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment) - Telephone/Online PBS Authorities | | | | | |
| Administration 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> | | | | | |
| Administrative Advice: <i>No increase in the maximum quantity or number of units may be authorised.</i> | | | | | |
| Administrative Advice: <i>No increase in the maximum number of repeats may be authorised.</i> | | | | | |
| Administrative Advice: <i>Special Pricing Arrangements apply.</i> | | | | | |
| Episodicity: Resected | | | | | |
| Severity: [blank] | | | | | |
| Condition: Non-small cell lung cancer (NSCLC) | | | | | |
| Restriction Summary / Treatment of Concept: | | | | | |
| Indication: Resected non-small cell lung cancer (NSCLC) | | | | | |
| Treatment Phase: Adjuvant therapy <i>Initial treatment</i> | | | | | |
| Population Clinical criteria: | | | | | |
| Patient must be both: (i) initiating treatment, (ii) untreated with an Anaplastic Lymphoma Kinase-Tyrosine Kinase Inhibitor (ALK-TKI) for non-small cell lung cancer; OR | | | | | |
| Patient must be continuing existing PBS-subsidised treatment with this drug; OR | | | | | |
| Patient must be both: (i) transitioning from existing non-PBS to PBS-subsidised supply of this drug, (ii) untreated with ALK-TKI at the time this drug was initiated. | | | | | |
| AND | | | | | |
| Clinical criteria | | | | | |
| The condition must be at least one of: (i) node positive, (ii) at least 4 cm in size, | | | | | |
| AND | | | | | |
| Clinical criteria | | | | | |
| The treatment must be for the purpose of adjuvant therapy following surgical resection, | | | | | |
| AND | | | | | |
| Clinical criteria | | | | | |

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| | |
|--|---|
| | Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing, |
| | AND |
| | Clinical criteria |
| | Patient must have have had a WHO performance status of no greater than 1 at treatment initiation with this drug, |
| | AND |
| | Clinical criteria |
| | The treatment must be as monotherapy |
| | AND |
| | Clinical criteria |
| | The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition |
| | AND |
| | Treatment criteria: |
| | Patient must be undergoing treatment that does not occur beyond the following, whichever comes first: (i) the first instance of disease progression/recurrence, (ii) 24 months in total for this condition from the first administered dose; mark any remaining repeat prescriptions with the words 'cancelled' where (i)/(ii) has occurred. |
| | 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). |
| | Administration advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. |
| | |
| Restriction Summary / Treatment of Concept: | |
| | Indication: Resected non-small cell lung cancer (NSCLC) |
| | Treatment Phase: Continuing treatment |
| | Clinical criteria: |
| | Patient must have previously received PBS-subsidised treatment with this drug for this indication |
| | AND |
| | Clinical criteria |
| | The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition |
| | AND |
| | Clinical criteria: |
| | Patient must be undergoing treatment that does not occur beyond the following, whichever comes first: (i) the first instance of disease progression/recurrence, (ii) 24 months in total for this indication from the first administered dose (regardless of whether treatment was PBS or non-PBS subsidised); mark any remaining repeat prescriptions with the words 'cancelled' where (i)/(ii) has occurred. |
| | |
| Restriction Summary / Treatment of Concept: | |
| | Indication: Resected non-small cell lung cancer (NSCLC) |
| | Treatment Phase: Grandfathering (transitioning from non-PBS to PBS subsidised treatment) |
| | Clinical criteria |
| | Patient must have received non-PBS treatment with this drug for this condition prior to [date of PBS listing] |

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| | |
|--|---|
| | AND |
| | Clinical criteria |
| | Patient must be untreated with ALK-TKI for non-small cell lung cancer prior to commencing treatment with this drug for this indication |
| | AND |
| | Clinical criteria |
| | The condition must have been at least one of: (i) node positive, (ii) at least 4 cm in size, |
| | AND |
| | Clinical criteria |
| | The treatment must have been for the purpose of adjuvant therapy following surgical resection, |
| | AND |
| | Clinical criteria |
| | Patient must have had evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing, |
| | AND |
| | Clinical criteria |
| | The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition |
| | AND |
| | Clinical criteria |
| | Patient must have had a WHO performance status of no greater than 1 at treatment initiation with this drug |
| | AND |
| | Clinical criteria: |
| | Patient must be undergoing treatment that does not occur beyond the following, whichever comes first: (i) the first instance of disease progression/recurrence, (ii) 24 months in total for this indication from the first administered dose (regardless of whether treatment was PBS or non-PBS subsidised); mark any remaining repeat prescriptions with the words 'cancelled' where (i)/(ii) has occurred. |
| | Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the 'Continuing treatment' criteria. |
| | Administrative Advice: This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria. |

Flow on changes:

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|---|------------------|-------------------|-------------------|----------------|------------------|
| ALECTINIB | | | | | |
| alectinib 150 mg capsule, 4 x 56 | 11226W | 1 | 224 | 3 | Alecensa |
| Restriction Summary / Treatment of Concept: | | | | | |
| Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) | | | | | |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | | |
| Administration advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
| Administrative Advice: No increase in the maximum quantity or number of units may be authorised. | | | | | |

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| | |
|--|--|
| | Administrative Advice: No increase in the maximum number of repeats may be authorised. |
| | Administrative Advice: Special Pricing Arrangements apply. |
| | Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment) - Telephone/Online PBS Authorities |
| Restriction Summary / Treatment of Concept: | |
| | Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) |
| | Treatment Phase: Initial treatment |
| | Clinical criteria: |
| | <i>Patient must be untreated with this drug for non-small cell lung cancer</i> |
| | AND |
| | Clinical criteria: |
| | The treatment must be as monotherapy |
| | AND |
| | Clinical criteria: |
| | The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC |
| | AND |
| | Clinical criteria: |
| | Patient must have a WHO performance status of 2 or less |
| | AND |
| | Clinical criteria: |
| | Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing |
| Restriction Summary / Treatment of Concept: | |
| | Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) |
| | Treatment Phase: Continuing treatment |
| | Clinical criteria: |
| | The treatment must be as monotherapy |
| | AND |
| | Clinical criteria: |
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition <i>indication</i> |
| | AND |
| | Clinical criteria: |
| | Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition |

- 3.2 The Pre-Sub-Committee Response (PSCR) agreed with the Secretariat’s suggestion of separating the restrictions into different phases of treatment (i.e. initial, continuing, and grandfathered patients) for easier administration by Services Australia.
- 3.3 The requested PBS restriction positioned alectinib as first-line adjuvant therapy in resected ALK-positive NSCLC. The pre-PBAC response noted that key international clinical practice guidelines including NCCN, ESMO and ASCO recommend sequential ALK TKI therapy for sustained ALK inhibition in ALK-positive disease in the metastatic setting (NCCN 2025, Hendriks 2023, Owen 2024). The pre-PBAC response stated that the PBS listing of alectinib in the adjuvant setting should not preclude treatment with

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an efficacious ALK TKI (including lorlatinib, brigatinib, and alectinib) upon progression to locally advanced/metastatic NSCLC.

- 3.4 The requested ex-manufacturer price (AEMP) (\$6,320.43) was the same as the current published AEMP for ALK-positive NSCLC stage IIIB (locally advanced) or stage IV (metastatic).
- 3.5 The requested PBS restriction did not specify tumour staging, (i.e., stage IB (tumours ≥ 4 cm) to stage IIIA), and instead, proposed tumour ‘at least 4 cm in size’. This was consistent with nivolumab¹ in neoadjuvant ‘resectable NSCLC’ (PBS items 14232C and 14233D) (i.e., stage agnostic) but not with atezolizumab² in adjuvant ‘resected early-stage (Stage II to IIIA) NSCLC’ (PBS items 13174J, 13172G) or osimertinib³ in ‘stage IB, II or IIIA NSCLC’ (PBS item 14168Q).
- 3.6 The requested PBS restriction and the TGA indication were slightly broader than the clinical evidence presented. The ALINA trial included participants with American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC) 7th edition of staging, adjuvant treatment in resected ALK-positive NSCLC stage IB (tumours ≥ 4 cm or node positive) to stage IIIA whereas the proposed restriction was for (i) node positive, or (ii) tumour at least 4 cm in size (i.e., stage agnostic). The ESC considered the proposed restriction was appropriate and sufficiently aligned with the ALINA trial.

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

4 Population and disease

- 4.1 Lung cancer is the fifth most commonly diagnosed cancer and the leading cause of cancer death in Australia.⁴ In ALK-positive NSCLC, the ALK gene undergoes a rearrangement within chromosome 2, resulting in the expression of an oncogenic ALK fusion protein which mediates constitutive kinase activity.⁵ The pre-PBAC response noted that ALK-positive NSCLC is a distinct molecular subtype where disease progression often remains ALK-driven.
- 4.2 The submission stated that the prevalence of ALK was estimated to be approximately 4.4% in Australian patients with NSCLC.⁶ This equated to a total of 82 eligible incident patients in 2025.

¹ Para. 5.1, nivolumab, Public Summary Document (PSD), July 2023 PBAC Meeting.

² Para. 7.1, atezolizumab, PSD, July 2022 PBAC Meeting

³ Para. 7.1, osimertinib, PSD, November 2023 PBAC Meeting

⁴ Australian Government (2020) Cancer Australia. Lung cancer in Australia.

⁵ Soda M, Choi YL, Enomoto M, et al. (2007) Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature* 448: 561-566.

⁶ Australian Government. Services Australia. Medicare Benefits Schedule statistics. 2025

http://medicarestatistics.humanservices.gov.au/statistics/mbs_item.jsp. This was based on calendar year 2019 to 2023 MBS processed claims data for MBS items 73341 and 73337.

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- 4.3 ALK-positive NSCLC tends to occur in younger females, with never or light smoking history compared with the general NSCLC population.⁷
- 4.4 ALK-positive NSCLC is associated with a high propensity of developing central nervous system metastases compared to ALK-negative disease, with 50-60% of patients expected to develop these metastases over the course of their disease.⁸
- 4.5 There were currently no targeted treatments reimbursed for patients with ALK-positive early-stage NSCLC. The standard of care for patients with early-stage NSCLC was complete surgical resection followed by adjuvant platinum-based chemotherapy. The benefit of adjuvant platinum-based chemotherapy is modest and the proportion of patients who experience disease recurrence or who die after surgery remains high.⁹
- 4.6 Alectinib is a highly selective and potent tyrosine kinase inhibitors (TKI) that targets ALK and rearranged during transfection (RET) tyrosine kinase. ALK-TKIs have successfully been used as treatment in the locally advanced/metastatic NSCLC setting, however, there has been a lack of studies evaluating the efficacy and safety of ALK-TKIs in earlier stages of the disease.

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

5 Comparator

- 5.1 The submission nominated platinum-based chemotherapy as the main comparator. The ESC considered the comparator was reasonable.
- 5.2 The submission stated that cisplatin-based chemotherapy is preferred but carboplatin may be used when cisplatin cannot be tolerated, or comorbidities exist. The majority of patients in the control arm (80%) were treated with cisplatin-pemetrexed in the ALINA trial. This was also aligned with clinician feedback from the National Lung Cancer Advisory Board, who advised that a platinum-agent in combination with pemetrexed is the current Australian standard of care for patients with resected ALK-

⁷ Shaw AT, Yeap BY, Mino-Kenudson M, et al. (2009) Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 27: 4247-4253; Chia PL, Mitchell P, Dobrovic A, et al. (2014) Prevalence and natural history of ALK positive non-small-cell lung cancer and the clinical impact of targeted therapy with ALK inhibitors. *Clin Epidemiol* 6: 423-432; Zhao F, Xu M, Lei H, et al. (2015) Clinicopathological characteristics of patients with non-small-cell lung cancer who harbor EML4-ALK fusion gene: a meta-analysis. *PLoS One* 10: e0117333; Mori M, Hayashi H, Fukuda M, et al. (2019) Clinical and computed tomography characteristics of non-small cell lung cancer with ALK gene rearrangement: Comparison with EGFR mutation and ALK/EGFR-negative lung cancer. *Thorac Cancer* 10: 872-879.

⁸ Johung KL, Yeh N, Desai NB, et al. (2016) Extended Survival and Prognostic Factors for Patients With ALK-Rearranged Non-Small-Cell Lung Cancer and Brain Metastasis. *J Clin Oncol* 34: 123-129; Shi W and Dicker AP. (2016) CNS Metastases in Patients With Non-Small-Cell Lung Cancer and ALK Gene Rearrangement. *Journal of Clinical Oncology* 34: 107-109; Rangachari D, Yamaguchi N, VanderLaan PA, et al. (2015) Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer* 88: 108-111.

⁹ Pignon JP, Tribodet H, Scagliotti GV, et al. (2008) Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol* 26: 3552-3559.

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positive early-stage NSCLC.¹⁰ This was consistent with the economic model and financial estimates.

5.3 The main arguments provided in support of this nomination were:

- There are currently no targeted treatments available to patients with resected ALK-positive early-stage NSCLC. Therefore, these patients are treated similarly to patients with resected early-stage NSCLC whose tumours do not have oncogenic driver alterations.
- There was consensus amongst international clinical practice guidelines, including Australian specific guidelines, that the standard of care for these patients was adjuvant therapy with platinum-based chemotherapy.^{11,12,13,14,15,16}
- An Advisory Board advised that a platinum agent in combination with pemetrexed was the current Australian standard of care for patients with resected ALK-positive early-stage NSCLC.¹⁷

5.4 The submission stated that the stage inclusion criteria for the ALINA trial were as per the AJCC/UICC 7th edition.¹⁸ However, under the AJCC/UICC 8th and proposed 9th edition, the eligible ALINA trial population would effectively become stage IB (tumour size equal to 4 cm) to IIIA and select IIIB. Thus, there was overlap in the PBS restrictions for other medicines for 'stage IIIB' ALK-positive NSCLC: crizotinib (10322G, 10323H); brigatinib (11976H, 11974F, 11980M, 11984R); ceritinib (11056X); and lorlatinib (12096P). However, these medicines would not be considered relevant comparators as they were not PBS restricted for use in the adjuvant setting.

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

¹⁰ Roche National Lung Cancer Advisory Board (2023). Digital Advisory Board Minutes.

¹¹ Tanel J, Spicer J, Chu Q, et al. (2023) Canadian Consensus Recommendations for the Management of Operable Stage II/III Non-Small-Cell Lung Cancer: Results of a Modified Delphi Process. *Curr Oncol* 30: 10363-10384.

¹² Cancer Council Australia. (2022) Clinical practice guidelines for the treatment of lung cancer.

¹³ Pisters K, Kris MG, Gaspar LE, et al. (2022) Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I-III A Completely Resected Non-Small-Cell Lung Cancer: ASCO Guideline Rapid Recommendation Update. *J Clin Oncol* 40: 1127-1129.

¹⁴ Kris MG, Gaspar LE, Chaft JE, et al. (2017) Adjuvant Systemic Therapy and Adjuvant Radiation Therapy for Stage I to IIIA Completely Resected Non-Small-Cell Lung Cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. *J Clin Oncol* 35: 2960-2974.

¹⁵ Remon J, Soria JC and Peters S. (2021) Early and locally advanced non-small-cell lung cancer: an update of the ESMO Clinical Practice Guidelines focusing on diagnosis, staging, systemic and local therapy. *Ann Oncol* 32: 1637-1642.

¹⁶ Postmus PE, Kerr KM, Oudkerk M, et al. (2017) Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 28: iv1-iv21.

¹⁷ Roche National Lung Cancer Advisory Board, Digital Advisory Board Minutes, 2023.

¹⁸ The ALINA trial under the AJCC/UICC 7th edition is stage IB to IIIA NSCLC.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician described how the efficacy results of the ALINA trial for early disease mirrored the magnitude of benefit observed in the metastatic setting in the ALK positive NSCLC space and this magnitude was considered substantial and clinically significant to patients. The presentation stated that disease-free survival is a valuable and meaningful endpoint for understanding benefit of a treatment from both the patient and clinician perspective and that the disease-free survival curves in the ALINA trial show substantial separation. The PBAC also noted the clinician supported the opportunity for retreatment with alectinib or to sequence an alternate third generation drug such as lorlatinib, noting retreatment is available for other oncogene driven cancers, such as GIST. The clinical expert further noted more follow-up was required to better understand the length of time to relapse and type of recurrence. The PBAC considered that the sponsor hearing was very informative as it provided a clinical perspective on treating this uncommon subset of NSCLC. The PBAC noted there was no evidence available supporting retreatment with ALK-TKIs upon disease recurrence following adjuvant treatment.

Consumer comments

- 6.2 The PBAC noted and welcomed input from individuals (9), a health care professional (1) and organisations (4) [the Medical Oncology Group of Australia (MOGA), Rare Cancers Australia, Lung Foundation Australia, and ALK Positive Australia Inc.] via the Consumer Comments facility on the PBS website. The individual comments described how alectinib was perceived as a proactive treatment that would reduce the risk of metastases or disease recurrence, extend survival and time with family and friends. The input described alectinib as less burdensome to administer being a daily oral tablet and as more tolerable than currently available treatment and that it would increase the ability to lead a normal life with less stress and worry.
- 6.3 The input from organisations provided testimonies from numerous patients describing the severe and long-term side effects of current treatments which affect patients' ability to work, socialise or maintain engagement in the community. The input noted that early intervention could significantly change the disease prognosis and that current chemotherapies have limited efficacy and higher risk of adverse events. The input noted that current PBS restrictions for alectinib create significant disparity in access for early-stage patients compared to those with advanced disease. Being able to access a drug in tablet form and reducing the need for hospital visits was felt to allow patients to return to a more normal daily life.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its strong support for the alectinib submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the ALINA 1 trial. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit

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Scale (ESMO-MCBS) for alectinib, of A, acknowledging the treatment as curative, based on a comparison with platinum-based chemotherapy.

Clinical trials

- 6.5 The submission was based on one head-to-head trial comparing alectinib to platinum-based chemotherapy¹⁹ (N=257) (ALINA). The ALINA trial was an ongoing global, multicentre, open-label, phase III randomised controlled trial (RCT) that investigated the efficacy and safety of alectinib compared with platinum-based chemotherapy as adjuvant treatment in participants with resected ALK-positive stage IB (tumours ≥ 4 cm) to IIIA NSCLC (as classified according to the 7th edition of the Cancer Staging Manual of the AJCC/UICC).
- 6.6 Details of the trials presented in the submission are provided in Table 2.

¹⁹ The majority of patients in the control arm (80%) were treated with cisplatin-pemetrexed in the ALINA trial.

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Table 2: Trials and associated reports presented in the submission

| Trial ID | Protocol title/ Publication title | Publication citation |
|---|---|--|
| <p>ALINA (NCT03456076; EUCTR2017- 004331-37-DE)</p> | <p>Primary CSR Clinical Report: Study BO40336 (ALINA) - A Phase III, open-label, randomized study to evaluate the efficacy and safety of adjuvant alectinib versus adjuvant platinum-based chemotherapy in patients with completely resected Stage IB (tumours ≥ 4 cm) to Stage IIIA anaplastic lymphoma kinase-positive non-small-cell lung cancer. Report No. 1118922.</p> <p>Statistical Analysis Plan: A Phase III, open-label, randomized study to evaluate the efficacy and safety of adjuvant alectinib versus adjuvant platinum-based chemotherapy in patients with completely resected Stage IB (tumours ≥ 4 cm) to Stage IIIA anaplastic lymphoma kinase-positive non-small-cell lung cancer. Version Number 2.</p> <p>Protocol: A Phase III, open-label, randomized study to evaluate the efficacy and safety of adjuvant alectinib versus adjuvant platinum-based chemotherapy in patients with completely resected Stage IB (tumours ≥ 4 cm) to Stage IIIA anaplastic lymphoma kinase-positive non-small-cell lung cancer. Version Number 7.</p> <p>Wu Y, Dziadziuszko R, Ahn J. Alectinib in resected ALK-positive non-small cell lung cancer.</p> <p>Nishio M, Wu YL, Barlesi F. Health-related quality of life (HRQoL) results for adjuvant alectinib vs chemotherapy in patients with resected ALK non-small cell lung cancer (NSCLC): Data from ALINA.</p> <p>Shah R, Solomon B, Ahn J. 1018: ALINA: efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC).</p> <p>Solomon B, Ahn J, Barlesi F. ALINA: A phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB–IIIA anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC). <i>Journal of Clinical Oncology</i> 2019;37 (15): TPS8569-TPS8569</p> <p>Solomon B, Ahn J, Dziadziuszko R. LBA2 ALINA: Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer.</p> | <p>CSR for the ALINA trial November 2023</p> <p>SAP for the ALINA trial 28 February 2022</p> <p>Protocol for the ALINA trial 16 December 2021</p> <p><i>NEJM</i> 2024; 390(14):1265-1276</p> <p><i>Journal of Clinical Oncology</i> 2024; 42(16_suppl)</p> <p><i>Oncology Research and Treatment</i> 2024; 47:243-244</p> <p><i>Journal of Clinical Oncology</i> 2019; 37(15): TPS8569-TPS8569</p> <p><i>Annals of Oncology</i> 2023; 34 (suppl_2): S1254-S1335.</p> |

Source: Table 2.3, pp22-23 of the submission.

ALK=anaplastic lymphoma kinase; CSR=clinical study report; HRQoL=Health-related quality of life; NEJM=New England Journal of Medicine; NSCLC=Non-small cell lung cancer; SAP=Statistical analysis plan.

6.7 The key features of the direct randomised trial are summarised in Table 3.

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Table 3: Key features of the included evidence

| Trial | N | Design/ duration | Risk of bias | Patient population | Outcome(s) | Use in modelled evaluation |
|--|-----|--|--------------|---|--|---|
| Alectinib vs. platinum-based chemotherapy | | | | | | |
| ALINA | 257 | R, OL, MC, alectinib 600 mg for 2 years or platinum-based chemotherapy (21 days x 4 cycles) as adjuvant therapy. Median duration of follow-up of 27.8 months (at CCOD) | Moderate | Age ≥18 Complete resection of histologically-confirmed, stage IB (tumour ≥4 cm) to stage IIIA NSCLC ^a Documented ALK-positive disease according to an FDA-approved and CE-marked test ECOG PS of Grade 0 or 1 | Primary: INV-DFS Secondary: OS, safety Exploratory: CNS-DFS, SF-36v2 | INV-DFS, LRR and death in the early-stage NSCLC setting used in economic model. |

Source: Compiled during the evaluation from p24, p27, Table 2.6, p29 and p64 of the submission

ALK = anaplastic lymphoma kinase; CCOD = Clinical cut-off date; CE = Conformité Européenne; CNS = Central nervous system; DFS = Disease-free survival; ECOG = Eastern Cooperative Oncology Group; FDA = Food and Drug Administration; INV = investigator assessed; LRR = Locoregional recurrence; MC = Multicentre; NSCLC = Non-small cell lung cancer; OL = Open-label; OS = Overall survival; PS = Performance scale; R = randomised; SF-36v2 = Short Form 36-item health survey

^a As classified according to the 7th edition of the Cancer Staging Manual of the American Joint Committee on Cancer (AJCC) and Union for International Cancer Control (UICC).

6.8 The submission stated that the ALINA trial had a low risk of bias. The evaluation considered a moderate risk of bias was more appropriate for the following reasons:

- Participants and investigators were not blinded to the treatment allocation. Most efficacy results were investigator assessed, including the primary outcome: investigator led disease-free survival (INV-DFS); secondary outcomes: overall survival (OS), and time to central nervous system (CNS) recurrence or death (CNS-DFS). Consequently, INV-DFS and subjective outcome measures (e.g., Short Form survey 36 items, Version 2 (SF-36v2) and reporting of adverse events may be biased, unlike those assessed by the independent data monitoring committee (iDMC). The iDMC assessed the prespecified DFS interim analysis when the stopping boundaries were crossed. This interim analysis became the primary analysis. Overall, the DFS results were similar between the investigator and blinded independent central review assessments.²⁰
- Attrition bias: The total percentage of major protocol deviations was high, although similar across arms (35.4% in the alectinib vs. 31.5% in the chemotherapy arm) with the most common major violation being the omission of a disease assessment (14.6% in the alectinib arm vs. 18.1% in the chemotherapy arm). The impact of missing scheduled tumour assessments on DFS was assessed by sensitivity analyses. Only the primary outcome was assessed by sensitivity analyses.

²⁰ Study BO40336 (ALINA) Retrospective Blinded Independent Central Review (BIRC) of Disease-Free Survival Data November 2023 referred to the BIRC and not the iDMC.

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- Other sources of bias: A formal cross-over design was not built into the trial. Subsequent treatment after disease recurrence was entirely at the discretion of the investigator. After disease reoccurrence in the alectinib arm, chemotherapy (12%) was most commonly prescribed followed by alectinib (4%). In the chemotherapy arm, alectinib (23%) was most commonly prescribed followed by radiotherapy (7%) then chemotherapy (5%). It was unknown if systemic treatments were given concurrently with radiotherapy, as participants may have received more than one subsequent anti-cancer therapy. Cross-over between the treatment arms was likely to bias the overall survival results towards the null.
 - The ALINA trial permitted the use of both central and local laboratory testing modalities.
- 6.9 The central ALK-testing result was determined to be ALK-negative for 6.3% (6 participants) in the alectinib arm and 9.3% (8 participants) in the chemotherapy arm. These participants were included in the analysis. The variability in testing approaches led to false-positive identifications and, consequently, affected the interpretation of the therapeutic efficacy; the results would likely be biased in favour of chemotherapy (which does not depend on ALK status).
- 6.10 While the ALINA trial had an eligibility criterion of randomisation within 12 weeks the PSCR stated that the timeframe for PBS-reimbursed treatment eligibility should be decided by the treating oncologist.
- 6.11 There was a lower frequency of adverse events leading to treatment discontinuation in the alectinib arm (5.5%) compared with the chemotherapy arm (12.5%). Alectinib adverse events required dose reduction in more than one-third of patients (see Comparative harms).
- 6.12 Standard endpoints used in oncology studies (including DFS and overall survival) were used to assess efficacy and safety in the ALINA trial. The submission stated that DFS has increasingly been used in the adjuvant setting as a surrogate for overall survival in early-stage NSCLC. The submission stated that the PBAC recommended osimertinib and atezolizumab based on primary DFS results from IMpower010 and ADAURA with immature overall survival data (para. 7.1, osimertinib, Public Summary Document [PSD], November 2023 PBAC Meeting; para. 7.1, atezolizumab, PSD, November 2023 PBAC Meeting). In both instances, the final overall survival dataset showed a consistent trend in benefit with the DFS findings.
- 6.13 The submission nominated a hazard ratio of 0.60 as the minimal clinically important difference (MCID) for DFS. The MCID was based on the European Society for Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (MCBS) and 2 positive recommendations by the PBAC for 2 other adjuvant therapies in early-stage NSCLC. The submission justified the choice of MCID by referencing the PSDs for atezolizumab and osimertinib, which reference the ESMO-MCBS. Applying the ESMO-MCBS scale to the DFS event for alectinib, compared to platinum-based chemotherapy, resulted in a

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Grade A rating. This was the highest grade (out of C, where A and B represent the grades with substantial improvement for new approaches to adjuvant therapy or new potentially curative therapies). The ESMO-MCBS does not define an explicit MCID but sets clear criteria for substantial clinical benefit. For patient reported outcomes, the submission proposed the minimal important difference (MID) for measures of mental and physical treatment benefits based on the SF-36v2, the User's Manual.²¹

Comparative effectiveness

- 6.14 In the ALINA trial, the primary efficacy objective was tested hierarchically in 2 populations: First in the resected ALK-positive stage II-III A NSCLC subpopulation; then in the Intention-to-treat (ITT) population (resected ALK-positive stage IB (tumours ≥ 4 cm) to III A NSCLC). As the stopping boundaries were crossed at the prespecified interim analysis, the interim analysis became the primary analysis. Due to the positive result at the interim analysis most participants had only received alectinib therapy for 18 months (87.5%) and not the estimated duration of 24 months (21.9%) requested in the PBS restriction.
- 6.15 The INV-DFS, blinded independent central review²² DFS and the overall survival results are summarised in Table 4. The INV-DFS Kaplan-Meier curves are presented in Figure 1.

²¹ Maruish ME. User's Manual for the SF-36v2 Health Survey (3rd edition). Quality Metric Incorporated 2011.

²² Study BO40336 (ALINA) Retrospective Blinded Independent Central Review (BIRC) of Disease-Free Survival Data November 2023 referred to the BIRC and not the iDMC.

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Table 4: Summary of survival outcomes in the ALINA trial

| | Alectinib n/N (%) | Chemotherapy n/N (%) | Absolute difference | HR (95% CI) |
|---|----------------------|-------------------------|-----------------------|--|
| INV-DFS (ITT) interim analysis at CCOD^a | | | | |
| Events, n (%) | 15/130 (11.5) | 50/127 (39.4) | 27.9% ^b | 0.24 (0.13, 0.43) P<0.0001 |
| Median DFS, months (95% CI) | NE (NE, NE) | 41.3 (28.5, NE) | NE | |
| K-M landmark estimates (% of participants INV-DFS at time points): | | | | |
| % not progressed at 24 months (95% CI) | 93.6 (89.4, 97.9) | 63.7 (54.6, 72.9) | 29.9% (19.8, 40.0) | P<.0001 |
| % not progressed at 36 months (95% CI) | 88.7 (81.8, 95.6) | 54.0 (43.7, 64.2) | 34.7% (22.4, 47.1) | P<.0001 |
| % not progressed at 48 months (95% CI) | 77.3 (65.0, 89.5) | 46.2 (34.2, 58.3) | 31.0% (13.8, 48.3) | P=0.0004 |
| BICR-DFS (ITT) interim analysis at CCOD^a | | | | |
| Events, n (%) | 16/130 (12.3) | 39/127 (30.7) | 18.4% | 0.30 (0.17, 0.54) P<0.0001 |
| Median DFS, months (95% CI) | NE (NE, NE) | NE (37.4, NE) | NE | |
| K-M landmark estimates (% of participants BICR-DFS at time points): | | | | |
| % not progressed at 24 months (95% CI) | 92.0 (87.2, 96.8) | 71.3 (62.5, 80.1) | 20.7 (10.7, 30.7) | P<.0001 |
| % not progressed at 36 months (95% CI) | 88.5 (81.7, 95.2) | 61.3 (50.6, 71.9) | 27.1 (14.6, 39.8) | P<.0001 |
| % not progressed at 48 months (95% CI) | 75.3 (61.6, 89.1) | 51.4 (37.6, 65.2) | 23.9 (4.4, 43.5) | P=0.0161 |
| Overall survival | | | | |
| Deaths, n/N (%) | 2/130 (1.5) | 4/127 (3.1) | 1.6% | - |
| Median months OS (95% CI) | NE (NE) | NE (NE) | NE | 0.46 (0.08, 2.52) P=0.3603 ^c |

Source: Table 2.14, p39; Table 2.15, p40 of the submission and Appendix 2, pp10-11 of Study BO40336 (ALINA) Retrospective Blinded Independent Central Review of Disease-Free Survival Data November 2023.

BICR= Blinded independent central review; CCOD=Clinical cut-off date; CI=confidence interval; INV-DFS=Investigator assessed disease-free survival; HR=hazard ratio; ITT=Intent-to-treat; K-M=Kaplan-Meier; N=number randomised; NE=not estimable; OS=Overall survival.

a Snapshot Date: 03AUG2023, Clinical Data Cut-off Date: 26JUN2023.

b The relative risk reduction was 76%

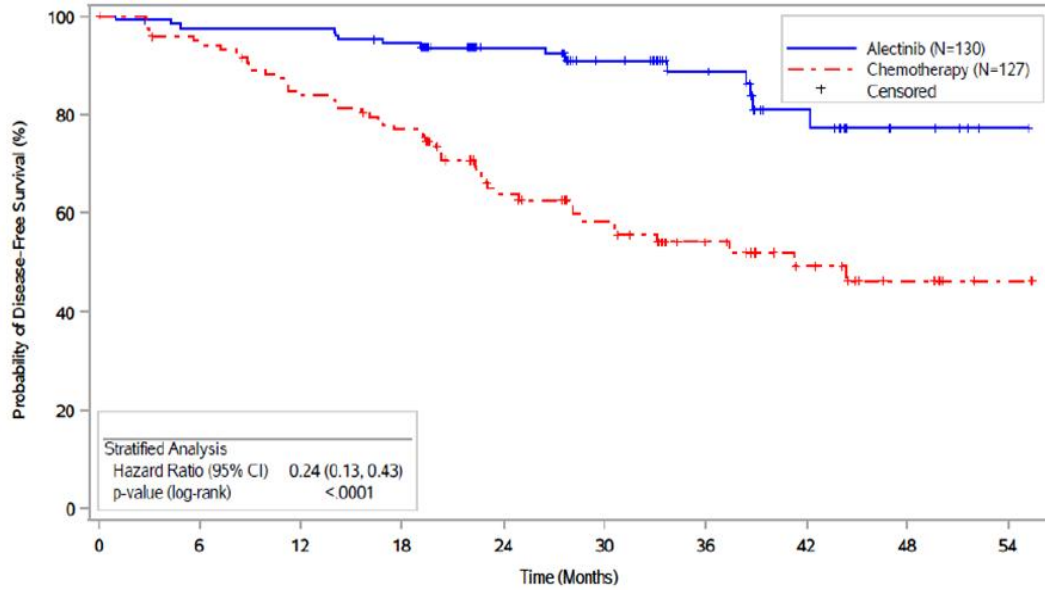
c Overall survival was not formally tested.

Summaries of DFS (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: race from IxRS (Asian vs. non-Asian) and stage from IxRS (IB vs. II vs. IIIA). Hazard ratios were estimated by Cox regression.

Absolute difference calculated post hoc during the evaluation.

Bold indicates statistically significant results.

Figure 1: Kaplan-Meier plot of investigator led disease-free survival (INV-DFS)



| Patients remaining at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
|----------------------------|-----|-----|-----|-----|----|----|----|----|----|----|
| Alectinib | 130 | 123 | 123 | 118 | 74 | 55 | 39 | 22 | 10 | 3 |
| Chemotherapy | 127 | 112 | 98 | 89 | 55 | 41 | 27 | 18 | 11 | 2 |

Source: Figure 2.4, p40 of the submission.

- 6.16 In the ALINA trial, at the prespecified interim analysis (clinical cut-off date (CCOD): 26 June 2023), the stratified hazard ratio for INV-DFS was 0.24 (95% CI: 0.13-0.43, $p < 0.001$) for alectinib compared with chemotherapy. The reduction in risk of disease recurrence or death was statistically significant. The hazard ratio of 0.24 was less than the proposed MCID of 0.60 representing substantial improvement.²³
- 6.17 Investigator assessed and blinded independent central review DFS analysis²⁴ showed comparable concordance with minimal difference between them, slightly favouring chemotherapy (see paragraph 6.4).
- 6.18 The median INV-DFS was not reached for alectinib compared with 41.3 months (95% CI: 28.5, NE) for chemotherapy. The Kaplan-Meier curves for INV-DFS began to separate at approximately 3 months after randomisation in favour of the alectinib arm and maintained thereafter (Figure 1).
- 6.19 There was a significantly higher proportion of participants alive and disease-free in the alectinib arm when compared to the chemotherapy arm at 24 months (93.6% vs. 63.7%, $p = 0.0001$ respectively), 36 months (88.7% vs. 54.0%, $p = 0.0001$ respectively) and 48 months (77.35% vs. 46.2%, $p = 0.0004$ respectively).

²³ Cherny N, Sullivan R, Dafni U, et al. (2015) A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). *Ann Oncol* 26: 1547-1573.

²⁴ Study BO40336 (ALINA) Retrospective Blinded Independent Central Review (BIRC) of Disease-Free Survival Data November 2023 referred to the BIRC and not the iDMC.

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- 6.20 In the ALINA trial, at the prespecified interim analysis (CCOD: 26 June 2023), the overall survival data were immature, with 98.5% vs. 96.9% alive in the alectinib and chemotherapy arms, respectively. The stratified hazard ratio for overall survival was 0.46 (95% CI: 0.08-2.52, p=0.3603). There was an additional death in the chemotherapy arm where only the year was reported for the date of death. This event was censored at the last date the participant was known to be alive. The median overall survival was not estimable. Further follow-up of overall survival was likely to be biased towards the null due to cross-over across the treatment arms.
- 6.21 Health-related quality of life (QoL) was assessed using the SF-36v2. Participants randomised to the chemotherapy arm could receive 4 (21-day) cycles of treatment whereas participants randomised to the alectinib arm could continue to receive treatment up to week 104. Due to this difference in the treatment schedules, patient reported outcome comparisons between arms were only made up to and including week 12.
- 6.22 In the ALINA trial, the mean change from baseline in the SF-36v2 Mental Component Summary score (MCS) at week 12 was 3.45 for alectinib versus -2.40 for chemotherapy (difference = 5.85). Similarly, the mean change in the SF36v2 Physical Component Summary score (PCS) at the same time point was 1.02 vs. -0.49 for alectinib and chemotherapy, respectively (difference = 1.52). Overall, the mean difference (MD) calculated post hoc during the evaluation, demonstrated that all domains exceeded the MID except for physical functioning (MD=-0.2) and PCS (MD=1.5).

Comparative harms

- 6.23 Table 5 summarises the overview of adverse events and deaths; and the treatment-related adverse events in the ALINA trial.

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Table 5: Summary of key adverse events in the trials

| Trial ID | Alectinib n with event/N (%) | Chemotherapy n with event/N (%) | RD (95% CI) |
|---|---------------------------------|------------------------------------|------------------|
| ALINA | | | |
| Type of adverse event, n (%) | | | |
| Any AE | 126 (98.4) | 112 (93.3) | 0.1 (0.0, 0.1) |
| Grade ≥3 AE | 38 (29.7) | 37 (30.8) | 0.0 (-0.1, 0.1) |
| Serious AE | 17 (13.3) | 10 (8.3) | 0.0 (0.0, 0.1) |
| Adverse events leading to discontinuation from treatment | 7 (5.5) | 15 (12.5) | -0.1 (-0.1, 0.0) |
| Treatment-related AE (any) | 120 (93.8) | 107 (89.2) | 0.0 (0.0, 0.1) |
| Treatment-related AE grade ≥3 AEs | 23 (18.0) | 33 (27.5) | -0.1 (-0.2, 0.0) |
| Treatment-related serious adverse events | 2 (1.6) | 8 (6.7) | -0.1 (-0.1, 0.0) |
| Treatment-related adverse events leading to discontinuation from treatment | 7 (5.5) | 14 (11.7) | -0.1 (-0.1, 0.0) |
| Treatment-related AE leading to dose modification /interruption | 49 (38.3) | 26 (21.7) | 0.2 (0.1, 0.3) |
| AEs leading to dose modification /interruption | 55 (43.0) | 27 (22.5) | 0.2 (0.1, 0.3) |
| Treatment-related adverse events | | | |
| Adverse events with a difference in incidence rate of at least 5% between treatment arms | | | |
| Nausea | 10 (7.8) | 87 (72.5) | 0.6 (0.7, 0.6) |
| Blood CPK increased | 55 (43.0) | 1 (0.8) | 0.4 (0.3, 0.5) |
| Constipation | 54 (42.2) | 30 (25.0) | 0.2 (0.1, 0.3) |
| AST increased | 53 (41.4) | 6 (5.0) | 0.4 (0.3, 0.5) |
| ALT increased | 43 (33.6) | 11 (9.2) | 0.2 (0.1, 0.3) |
| Blood bilirubin increased | 43 (33.6) | 1 (0.8) | 0.3 (0.2, 0.4) |

Source: Table 2.19, p44; Table 2.20, p44-45 of the submission.

AE=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CI=confidence interval; CPK=creatinine phosphokinase; n=number of participants reporting data; N=total participants in arm; RD=risk difference
Italics calculated during the evaluation.

- 6.24 The submission noted that the median duration of treatment was different between the 2 arms (23.9 months in the alectinib arm vs. 2.1 months in the chemotherapy arm).
- 6.25 The proportion of participants who experienced at least one grade ≥3 adverse event in the alectinib arm (29.7%) was comparable to the chemotherapy arm (30.8%). The proportion of participants who experienced at least one serious adverse event was 13.3% in the alectinib arm and 8.3% in the chemotherapy arm.
- 6.26 The 2 most frequent adverse event (≥30% of participants in either arm) were:
- Nausea (alectinib 7.8% vs. chemotherapy 72.5%).
 - Blood creatine phosphokinase (CPK) increased (alectinib 43.0% vs. chemotherapy 0.8%).
- 6.27 A total of 2 participants (1.6%) in the alectinib arm and 5 participants (4.2%) in the chemotherapy arm died. In the alectinib arm, both participants died due to disease

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recurrence. The causes of death for the 5 participants in the chemotherapy arm were disease recurrence (2 participants), bilateral pneumonia (one participant), COVID 19 (one participant) and unknown (one patient).

- 6.28 Treatment-related adverse events leading to dose modification/interruption were higher in the alectinib arm (38.8%) than the chemotherapy arm (21.7%), however, and this difference may have biased the DFS results. Dose reductions or interruptions were permitted by the investigator according to prespecified criteria (e.g. reductions in steps of 150 mg up to 2 times for drug-related toxicities, a dose below 300 mg was not allowed). This was consistent with the TGA Product Information.
- 6.29 Participants treated with alectinib were more likely to experience grade ≥ 3 increased blood CPK (alectinib: 6.3% vs chemotherapy: 0.8%). The ESC noted the alectinib arm had higher rates liver function test dysfunction, myalgia, dysgeusia and oedema. In contrast, participants treated with chemotherapy were more likely to experience grade ≥ 3 nausea (alectinib: 0% vs chemotherapy: 4.2%) and neutropenia (alectinib: 0% vs chemotherapy: 8.3%). The ESC noted higher rates of transient haematological dysfunction in the chemotherapy arm.
- 6.30 Generally, the submission claimed that the overall safety experience with alectinib in the ALINA trial was consistent with the safety profile in the locally advanced and metastatic setting and no new safety signals were identified.

Benefits/harms

- 6.31 A summary of the comparative benefits and harms for alectinib versus platinum-based chemotherapy is presented in Table 6.

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Table 6: Summary of comparative benefits and harms for alectinib and platinum-based chemotherapy

| Disease-free survival (duration of follow-up 24 months)^a | | | | |
|---|---|--|-------------------------------------|---|
| | Alectinib n/N (%) | Chemotherapy n/N (%) | Absolute Risk Difference | HR (95% CI) |
| Progressed, n (%) | 15/130 (11.5) | 50/127 (39.4) | -27.9% ^b | 0.24 (0.13, 0.43) P=<0.0001 |
| Median DFS, months (95% CI) | NE (NE, NE) | 41.3 (28.5, NE) | NE | |
| K-M landmark estimates (% of participants INV-DFS at time points): | | | | |
| % not progressed at 24 months (95% CI) | 93.6 (89.4, 97.9) | 63.7 (54.6, 72.9) | 29.9% (19.8, 40.0) | P=<.0001 |
| % not progressed at 36 months (95% CI) | 88.7 (81.8, 95.6) | 54.0 (43.7, 64.2) | 34.7% (22.4, 47.1) | P=<.0001 |
| % not progressed at 48 months (95% CI) | 77.3 (65.0, 89.5) | 46.2 (34.2, 58.3) | 31.0% (13.8, 48.3) | P=0.0004 |
| Overall survival (duration of follow-up 2 years) | | | | |
| Deaths, n/N (%) | 2/130 (1.5) | 4/127 (3.1) | 1.6% | 0.46 (0.08, 2.52) P=0.3603 ^b |
| Median OS, months (95% CI) | NE (NE) | NE (NE) | NE | |
| Harms | | | | |
| | Alectinib n with event/N (%) | Chemotherapy n with event/N (%) | Absolute Risk difference | RD (95% CI) |
| Type of adverse event, n (%) | | | | |
| Any AE | 126 (98.4) | 112 (93.3) | 5.1% | 0.1 (0.0, 0.1) |
| Treatment-related AE (any) | 120 (93.8) | 107 (89.2) | 4.6% | 0.0 (0.0, 0.1) |
| Grade ≥3 AE ^a | 38 (29.7) | 37 (30.8) | -1.1% | 0.0 (-0.1, 0.1) |
| Treatment-related adverse events | | | | |
| Adverse events with a difference in incidence rate of at least 5% between treatment arms | | | | |
| Nausea | 10 (7.8) | 87 (72.5) | -64.7 | 0.6 (0.7, 0.6) |
| Blood CPK increased | 55 (43.0) | 1 (0.8) | 42.2 | 0.4 (0.3, 0.5) |
| Constipation | 54 (42.2) | 30 (25.0) | 17.2 | 0.2 (0.1, 0.3) |
| AST increased | 53 (41.4) | 6 (5.0) | 36.4 | 0.4 (0.3, 0.5) |
| ALT increased | 43 (33.6) | 11 (9.2) | 24.4 | 0.2 (0.1, 0.3) |
| Blood bilirubin increased | 43 (33.6) | 1 (0.8) | 32.8 | 0.3 (0.2, 0.4) |

Source: Table 2.14, p39; Table 2.15, p40; Table 2.19, p44; Table 2.20, p44-45 of the submission.

AE=adverse events; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CCOD=Clinical cut-off date; CI=confidence interval; CPK=creatinine phosphokinase; INV-DFS=investigator disease-free survival; HR=hazard ratio; ITT=Intent-to-treat; KM=Kaplan-Meier; N=number randomised; NE=not estimable; RD=risk difference

Summaries of DFS (median, percentiles) were Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Strata are: race from IxRS (Asian vs. non-Asian) and stage from IxRS (IB vs. II vs. IIIA). Hazard ratios were estimated by Cox regression.

a Snapshot Date: 03AUG2023, Clinical Data Cut-off Date: 26JUN2023.

b The relative risk reduction was 76%.

Absolute difference calculated post hoc during the evaluation.

Bold indicates statistically significant results.

6.32 On the basis of direct evidence presented by the submission, for every 100 patients treated with alectinib in comparison with platinum-based chemotherapy:

- Approximately 30 additional patients will remain disease-free at 2 years, however, there would be no difference in overall survival after 2 years.

6.33 On the basis of direct evidence presented by the submission, for every 100 patients treated with alectinib in comparison with platinum-based chemotherapy over a duration of follow-up 24 months:

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- Approximately 6 additional patients would experience an adverse event or treatment-related adverse event.
- Approximately 65 fewer patients would experience nausea.
- Approximately 43 additional patients would experience increased blood creatine phosphokinase.
- Approximately 18 additional patients would experience constipation.
- Approximately 37 additional patients would experience increased aspartate aminotransferase.
- Approximately 25 additional patients would experience increased alanine aminotransferase.
- Approximately 33 additional patients would experience increased blood bilirubin.

Clinical claim

- 6.34 The submission described alectinib as superior in terms of effectiveness compared to platinum-based chemotherapy. This claim was adequately supported. The key issues were the moderate risk of bias in the key trial and that the overall survival results were immature. The ESC considered some of the issues contributing to the risk of bias were unavoidable and that the uncertainty may bias results in both directions. Overall ESC considered the disease-free survival outcome was convincing, noting significant separation in the curves (see Figure 1). The ESC also considered, given the high use of effective therapies in the metastatic setting, the OS data would be uninterpretable even with longer follow-up.
- 6.35 The submission described alectinib as similar in terms of safety compared to platinum-based chemotherapy. This claim was adequately supported. The ESC noted toxicities were well known and mild for both the intervention and comparator.
- 6.36 The PBAC considered that the claim of superior comparative effectiveness was reasonable and adequately supported by the data but did note that there was no signal of overall survival benefit at the prespecified DFS interim analysis.
- 6.37 The PBAC considered that the claim of non-inferior comparative safety was reasonable and adequately supported by the data but did note that the impact of adverse events from adjuvant alectinib would typically be substantially prolonged compared to the adverse events from the comparator of adjuvant chemotherapy, due to the difference in planned treatment durations (2 years compared to 12 weeks).

Economic analysis

- 6.38 The submission presented a cost-utility analysis. A summary of the model structure, key inputs and rationale is given in Table 7.

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Table 7: Summary of model structure, key inputs and rationale

| Component | Summary |
|----------------------------------|---|
| Treatments | <p>Adjuvant: alectinib vs platinum-based chemotherapy, cisplatin with pemetrexed. Locoregional recurrence: radiotherapy, chemotherapy. 1L DR: lorlatinib, alectinib, 2L DR: brigatinib, lorlatinib.</p> <p>The evaluation considered it as uncertain if it was appropriate to allow later line use of an alternative ALK-TKI if patients have had alectinib in the adjuvant setting. The PSCR (p4) noted key international clinical practice guidelines (including NCCN, ESMO and ASCO) recommend sequential ALK TKI therapy for sustained ALK inhibition in ALK-positive disease (NCCN 2025, Hendriks 2023, Owen 2024). The treatments received following locoregional recurrence, 1L and 2L DR may be reasonable, as they are based on current market shares and international guidelines. However, brigatinib is unlikely to be taken in 2L DR as this would represent the third drug in the same class. It is more likely that patients would receive chemotherapy. The PSCR (p2) argued the PBS restrictions for the ALK TKIs that are PBS listed in the locally advanced/metastatic NSCLC setting have no explicit limitations on eligibility based on previous ALK TKI treatments. Brigatinib was therefore argued to be a reasonable 2L DR treatment option.</p> |
| Type of analysis | Cost-effectiveness and cost-utility analysis. Appropriate. |
| Time horizon | <p>20 years in the model base case. The time horizon was relatively long compared to the median duration of follow-up in the ALINA trial (2.6 years). A 15-year time horizon may be more appropriate (para. 6.37, atezolizumab, PSD, July 2022 PBAC meeting and para. 6.28, osimertinib, PSD, November 2023 PBAC meeting). The ICER was sensitive to the time horizon. The ICER increased from \$ [redacted] ¹ to \$ [redacted] ² per QALY gained when the time horizon was changed from 20 years to 15 years.</p> |
| Methods used to generate results | Markov model. Reasonable. |
| Health states | <ol style="list-style-type: none"> 1. Disease-free survival (DFS) 2. Locoregional recurrence (LRR) 3. First-line distant recurrence (1L DR) 4. Second-line distant recurrence (2L DR) 5. Death <p>This was consistent with other models for NSCLC, which were considered reasonable (Table 11, atezolizumab, PSD, July 2022 PBAC meeting and Table 8, osimertinib, PSD, November 2023 PBAC meeting).</p> |
| Cycle length | One week. |
| Population | <p>Mean age 54.9 years. Adjuvant treatment in patients with resected ALK-positive stage IB (tumours ≥4 cm) to IIIA NSCLC. Represents the population in the ALINA trial.</p> |
| Transition probabilities | <ul style="list-style-type: none"> - INV-DFS, LRR and death in the early-stage NSCLC setting: ALINA trial. This was reasonable. - LRR to DR: Nakamichi et al (2017)²⁵ study investigating chemotherapy and radiotherapy. The study reported by Nakamichi et al. (2017) estimated the progression rate of patients with NSCLC that have had a LRR to 1L DR, and was accepted by the PBAC as the source for transitioning from the LRR to 1L DR health state in the economic model for adjuvant atezolizumab in NSCLC (Table 11, atezolizumab, PSD, July 2022 PBAC meeting). - 1L DR to 2L DR: ALEX trial. ALEX was an open-label trial of alectinib versus crizotinib in untreated advanced/metastatic ALK-positive NSCLC. The PBAC has not previously seen the ALEX trial in previous assessments of alectinib or crizotinib for NSCLC. - 1L DR to death: ALEX trial or general population mortality (ABS Life Tables). Source of data was inconsistent with costing of treatment in 1L DR. For example, the data for the transition probabilities from 1st line distant recurrence to death was taken from the ALEX trial of alectinib |

²⁵ Nakamichi S, Horinouchi H, Asao T, et al. (2017) Comparison of Radiotherapy and Chemoradiotherapy for Locoregional Recurrence of Non-small-cell Lung Cancer Developing After Surgery. Clin Lung Cancer 18: e441-e448.

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| Component | Summary |
|----------------------|---|
| | <p>versus crizotinib. However, the model costed for IL DR lorlatinib and alectinib in the alectinib and chemotherapy arms respectively.</p> <ul style="list-style-type: none"> - 2L DR to death: ALUR trial or general population mortality (ABS Life Tables). ALUR was an open-label trial of alectinib versus chemotherapy in crizotinib-pretreated ALK-positive NSCLC. The PBAC has previously seen the ALUR trial.²⁶ Source of data was inconsistent with costing of treatment in 2L DR. - LRR to death: The submission assumed 2 different sources of data; the weekly rate of 0.0046 for the chemotherapy arm was taken from Nakamichi et al (2017), and a much higher weekly rate of 0.111 for the alectinib arm was taken from the ALEX trial, where patients received alectinib. The ESC considered the use of different sources of data was selective and not well justified. Maximum of proportion of alive patients treated with alectinib with a LRR event (time-dependent) who die (ALEX trial) and general population mortality (ABS Life Tables). Applying both transition probabilities from Nakamichi et al (2017) increased the ICER from \$█████¹ to \$█████² per QALY gained. |
| Extrapolation method | <p>DFS was extrapolated using the log-logistic function. This function had the best fit to the data based on AIC (Akaike information criterion) and BIC (Akaike information criterion). The Kaplan-Meier curve was used up to 30.1 months.</p> <p>The log-logistic function assumption was reasonable. The ICER was moderately sensitive to the choice of function.</p> <p>The model assumed time independent transition probabilities from the other trials. This was reasonable.</p> <p>The economic model applied 2 adjustments to the extrapolated DFS: first, the model allowed the treatment effect of alectinib to decrease over time from no decrease at 5 years to treatment effect null at 10 years.</p> <ul style="list-style-type: none"> - The submission claimed that there was a lack of external evidence specific to the adjuvant NSCLC treatment setting to inform at what time point the treatment effect of alectinib ceases. The submission claimed that, consistent with the adjuvant atezolizumab submission to the PBAC (Atezolizumab, PSD, July 2022 PBAC meeting), the submission adopted a conservative approach and assumed the treatment effect started to decrease at year 5 and ceased at year 10. The treatment effect waning assumption was reasonable. The ICER was not sensitive to this parameter. Removing the treatment waning assumption, the ICER decreased from \$█████¹ to \$█████¹ per QALY gained. - The submission applied a cure adjustment where the model allowed patients to be considered cured if they were disease-free for a certain number of years. In the base case, the risk of recurrence started to decrease at 4 years and the minimum risk of recurrence was reached at 5 years, at which time it was assumed that if patients had not experienced recurrence then 92% of patients were cured. A 91% cure rate at 10 years was used in the model submitted to NICE based on discussions with UK clinicians using a modified structured expert elicitation method. The ICER was sensitive to the cure assumption. Changing the cure assumption to 91% cure rate at 10 years increased the ICER from \$█████¹ to \$█████³ per QALY gained. |
| Utilities | <p>DFS = on-treatment 0.813 (alectinib), 0.776 (chemotherapy) (ALINA trial) DFS = off-treatment 0.861 (alectinib), 0.847 (chemotherapy) (ALINA trial) LRR = 0.770 (Chouaid 2013)²⁷ 1L DR = 0.730 (Chouaid 2013) 2L DR = 0.660 (Chouaid 2013)</p> |

²⁶ Alectinib Public Summary Document (July 2017 PBAC meeting).

²⁷ Chouaid C, Agulnik J, Goker E, et al. (2013) Health-related quality of life and utility in patients with advanced non-small-cell lung cancer: a prospective cross-sectional patient survey in a real-world setting. J Thorac Oncol 8: 997-1003.

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| Component | Summary |
|------------------|--|
| | <p>The ESC considered application of different utilities across treatment arms in the DFS health state when patients are off-treatment was not appropriate. Applying a utility of 0.854 for both treatment arms increased the ICER from \$■■■■¹ to \$■■■■¹ per QALY gained.</p> <p>The economic evaluation did not apply utilities that decreased with age.</p> |
| Costs | <p>Alectinib (150 mg tablet) 600 mg (4 x 150 mg tablets) BID DPMQ \$■■■■, up to 2 years.</p> <p>Chemotherapy every 21 days for 4 cycles, 133 mg of cisplatin and 887 mg of pemetrexed per administration:</p> <ul style="list-style-type: none"> - Cisplatin (50 mg/50 mL, 50 mL vial) published DPMQ \$184.46 - Cisplatin (100 mg/100 mL, 100 mL vial) published DPMQ \$184.46 - Pemetrexed (100 mg vial) published DPMQ \$193.98 - Pemetrexed (500 mg vial) published DPMQ \$148.52 - Pemetrexed (1000 mg vial) published DPMQ \$193.98 <p>Medical services, such as CT scans were taken from relevant MBS items.</p> <p>The cost of management of adverse events was taken from NHCDC report version 11.0 2020-21.²⁸ This was reasonable.</p> <p>The costs in LRR included chemotherapy in the alectinib arm and radiotherapy in the chemotherapy arm. The cost of chemotherapy was as given for the chemotherapy arm above and the cost of radiotherapy was taken from Batumalai et al. (2019).²⁹ This was reasonable.</p> <p>On progression to 2L DR, patients in the alectinib arm were assumed to be treated with brigatinib. It is unlikely that patients would be treated with brigatinib, as this would be the third drug in this class. Patients are more likely to receive chemotherapy.</p> <p>The submission assumed median treatment durations for the costs of treatment in 1L and 2L DR. It was preferable to assume mean treatment durations.</p> <p>The submission estimated the effective prices of lorlatinib and brigatinib. The true effective prices are given in the Committee-in-Confidence section.</p> <p>The submission applied an end-of-life cost of \$6,409, representing the average monthly cost over the last 6 months of life. This was taken from the end-of-life care costs associated with lung cancer using participants in the Sax Institute’s 45 and Up Study, which was a longitudinal study of 267,153 people aged ≥45 years in New South Wales (Goldsbury et al 2020).³⁰ It was more appropriate to add the costs in the final 6 months of life, which gave a total of \$38,454. By far the greatest source of costs in Goldsbury et al (2020) related to hospital-based care (Figure 4, Goldsbury et al 2020). Therefore there was likely to be little double counting with PBS costs already included in the model. With the change of using the total cost of \$38,454, the ICER decreased from \$■■■■¹ to \$■■■■¹ per QALY gained</p> |
| Discounting | 5% per year for costs and benefits. This was appropriate. |
| Software package | Microsoft Excel 2016. Reasonable. |

Source: Table 3.2, p58-59 of the submission. *Text in italics from the evaluation.*

CT = computed tomography, DFS = disease-free survival, DPMQ = Dispensed Price for Maximum Quantity, ICER = incremental cost-effectiveness ratio, INV = investigator assessed, LRR = locoregional recurrence, MHCDC = National Hospital Cost Data Collection, NICE = National Institute for Health and Care Excellence, NSCLC = non-small cell lung cancer, PBAC = Pharmaceutical Benefits Advisory Committee, QALY = Quality-Adjusted Life-Year, 1L DR = 1st line distant recurrence, 2L DR = 2nd line distant recurrence.

²⁸ National Hospital Cost Data Collection (NHCDC) Public Sector Report 2020-21

<https://www.ihcpa.gov.au/resources/national-hospital-cost-data-collection-nhcdc-public-sector-report-2020-21>

²⁹ Batumalai V, Wong K, Shafiq J, et al. (2019) Estimating the cost of radiotherapy for 5-year local control and overall survival benefit. *Radiother Oncol* 136: 154-160.

³⁰ Goldsbury DE, Weber MF, Yap S, et al. (2020) Health services costs for lung cancer care in Australia: Estimates from the 45 and Up Study. *PLoS One* 15: e0238018.

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The redacted values correspond to the following ranges:

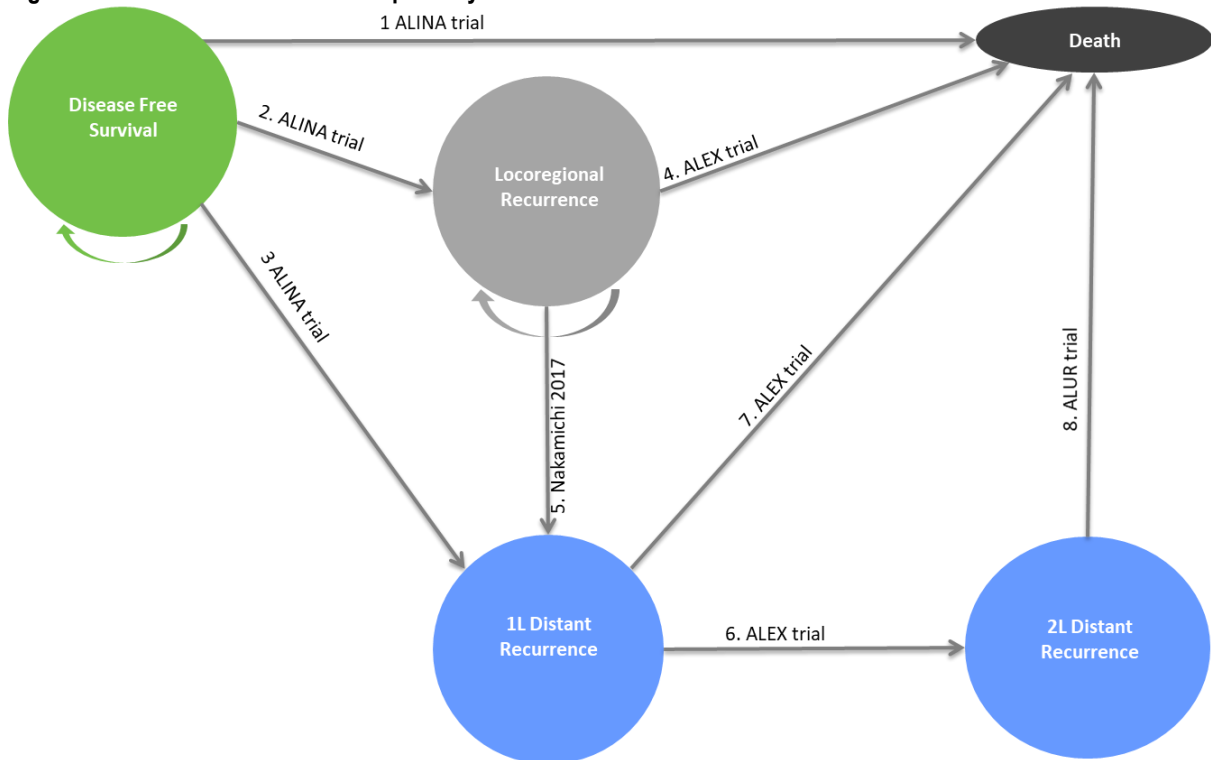
¹ \$25,000 to < \$35,000

² \$35,000 to < \$45,000

³ \$45,000 to < \$55,000

6.39 Figure 2 presents the health states and transition pathways in the economic model. The submission claimed that the economic model structure aligned with the treatment algorithm, reflected the disease course and was aligned with the economic model structure accepted by the PBAC in its positive recommendation for adjuvant atezolizumab in resected PD-L1 \geq 50% stage II-IIIa NSCLC and adjuvant osimertinib in resected epidermal growth factor receptor (EGFR)-mutation positive stage IB-IIIa NSCLC (atezolizumab, PSD, July 2022 PBAC meeting; osimertinib, PSD, November 2023 PBAC meeting). The ESC noted the figure did not accurately reflect the use of different data sources across treatment arms for the transition from LRR to Death (ALEX trial for the alectinib arm and Nakamichi 2017 for the chemotherapy arm).

Figure 2 Health states and transition pathways in the economic evaluation



Source: Figure 3.2, p64 of the submission.

6.40 The model time horizon was 20 years vs. 2.6 years in the ALINA trial. The PBAC preferred a 15-year time horizon in the atezolizumab (para. 6.37, atezolizumab, PSD, July 2022 PBAC meeting) and osimertinib (para. 6.28, osimertinib, PSD, November 2023 PBAC meeting) submissions. When the time horizon was decreased from the base case value of 20 years to 15 years, the ICER increased from \$25,000 to < \$35,000 to \$35,000 to < \$45,000 per quality-adjusted life-year (QALY) gained. The ESC noted 56% economic evaluations of adjuvant treatment of early-stage adjuvant NSCLC from the literature used a time horizon < 10 years. The ESC noted the

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PSCR emphasised the importance of the time horizon to adequately capture differences in outcomes and costs incurred throughout all stages of NSCLC. However, the ESC considered the precedent of 15 years from atezolizumab and osimertinib was appropriate as the shorter time horizon can be used to mitigate uncertainty in the estimated long-term costs and outcomes.

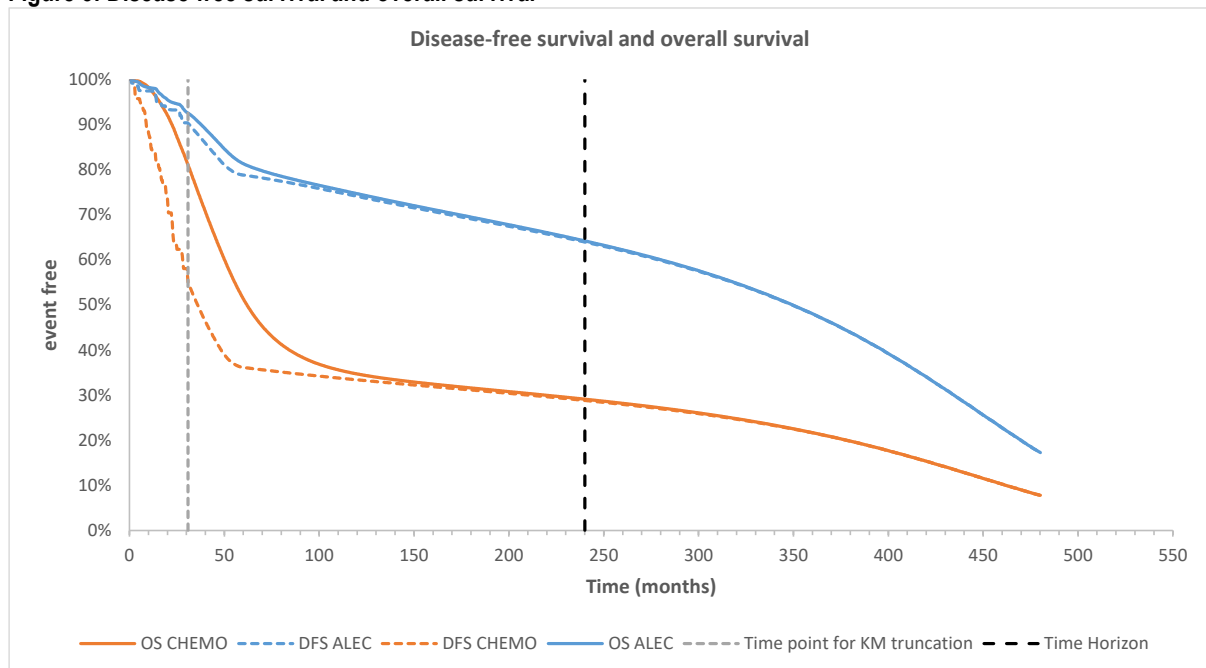
- 6.41 The submission assumed 2 different sources of data for the transition probabilities of LRR to death: the weekly rate of 0.0046 for the chemotherapy arm was taken from Nakamichi et al (2017), and a higher weekly rate of 0.111 for the alectinib arm was taken from the ALEX trial (open-label trial of alectinib vs crizotinib in patients with untreated advanced/metastatic ALK-positive NSCLC). The PSCR argued it is clinically reasonable to consider that a patient who received targeted treatment would receive a greater survival benefit compared with a patient who only received chemotherapy or radiotherapy. The ESC considered the use of different sources of data was selective and not well justified.
- 6.42 It was not clear why the submission assumed one data source (Nakamichi 2017) for transitions from LRR to 1L DR, but 2 different sources (Nakamichi 2017 and ALEX trial) for transitions from LRR to death. Furthermore, in the ALEX trial, patients were treated with alectinib. This was not appropriate as it was assumed that patients in the LRR health state received either chemotherapy or radiotherapy. Applying transition probabilities from Nakamichi 2017 (cell C27, worksheet “Transition Inputs” set to 0.0046) increased the ICER from \$25,000 to < \$35,000 to \$35,000 to < \$45,000 per QALY gained.
- 6.43 The data for the transition probabilities from 1L DR to 2L DR was taken from the ALEX trial of alectinib versus crizotinib. Specifically, the transition probability for the alectinib arm was assumed equal to that from the alectinib arm of the ALEX trial, and the transition probability for the chemotherapy arm was assumed equal to that from the crizotinib arm of the ALEX trial. However, the model costed for 1L DR lorlatinib and alectinib in the alectinib and chemotherapy arms respectively. Therefore, the costs and transition probabilities were not consistent. It would be preferable to source the transition probability for the alectinib arm from a trial of lorlatinib and to use the transition probability from alectinib from the ALEX trial for the chemotherapy arm. Furthermore, the weekly probability of transition from 1L DR to 2L DR for both the alectinib and chemotherapy treatment arms was incorrect. These values were very high, at 0.889 and 0.893 respectively. They were derived from the ratio of the number of 1L to 2L transitions, divided by the total number of events. Instead, the weekly probability of transition from 1L DR to 2L DR should be calculated based on the number of events and time over which the events occurred.
- 6.44 Similarly, the data for the transition probabilities from 1L DR to death was taken from the ALEX trial of alectinib versus crizotinib. However, the model costed for 1L DR lorlatinib and alectinib in the alectinib and chemotherapy arms respectively. Therefore, the costs and transition probabilities were not consistent. The PSCR noted that the PBAC had accepted the ALK tyrosine kinase inhibitors (TKIs; lorlatinib,

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brigatinib and alectinib) to be non-inferior in efficacy and safety in the locally advanced/metastatic NSCLC setting, and they are PBS listed on a cost-minimisation basis.

- 6.45 The transition probability of 2L DR to death of the alectinib treatment arm from the ALUR trial was allocated to both treatment arms in the adjuvant setting (i.e. alectinib and platinum-based chemotherapy arms) as the overall survival was not evaluable for chemotherapy patients in ALUR. However, the model costed for patients in the alectinib arm to receive brigatinib treatment, not alectinib treatment, in 2L DR and patients in the chemotherapy arm were costed to receive lorlatinib treatment, not alectinib treatment. Therefore, the treatments costed and the transition probabilities in the 2L DR setting were not consistent.
- 6.46 Disease-free survival and overall survival Figure 3 presents DFS and overall survival over time. The time horizon of the model was truncated at 20 years after initiation of adjuvant treatment with alectinib or chemotherapy. This showed that patients were predicted to spend the great majority of the time in the DFS health state, especially for the alectinib treatment arm.

Figure 3: Disease-free survival and overall survival



Source: Adapted from Figure 3.10 of the submission, "Alectinib" and "Chemo" worksheets of economic model. Chemo = chemotherapy, DFS = disease-free survival, KM = Kaplan-Meier, OS = overall survival.

- 6.47 Extrapolation beyond the available trial data across the model time horizon was performed by fitting parametric functions to the patient-level DFS results. Based on the AIC (Akaike Information Criterion), BIC (Bayesian Information Criterion) statistics and visual inspection, the log-logistic function was considered the overall best fit for DFS Kaplan-Meier data extrapolation of the alectinib and platinum-based

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chemotherapy treatment arms in the base case of the economic evaluation. The Esc considered this was reasonable.

- 6.48 The economic model applied 2 adjustments to the extrapolated DFS, including the limitation of treatment effect where the model allowed the treatment effect of alectinib to decrease over time and a cure adjustment where the model allowed patients to be considered cured (i.e. not experience recurrence or disease-related death) if they were disease-free for a certain number of years.
- Consistent with the adjuvant atezolizumab submission to the PBAC (Table 11, atezolizumab, PSD, July 2022 PBAC meeting), the economic model adopted a conservative approach and assumed the treatment effect started to decrease at year 5 and ceased at year 10. This was reasonable. Cost-effectiveness was minimally sensitive to the assumption of a treatment waning effect, as the base case ICER of \$25,000 to < \$35,000 per QALY gained decreased to \$25,000 to < \$35,000 per QALY gained when the assumption of waning effect was removed.
 - The submission applied a cure rate that began from Year 4 (i.e. 2 years after cessation of therapy) and increased linearly to a maximum of 92% at Year 5 for patients in the DFS health state in both the alectinib and chemotherapy arms. This yielded the modelled DFS as given in Figure 4. As can be seen from this figure, the cure assumption has a very large effect on the extrapolation of DFS. Cost-effectiveness was very sensitive to the assumption of a cure, as the base case ICER of \$25,000 to < \$35,000 per QALY gained increased to \$55,000 to < \$75,000 per QALY gained when the assumption of a cure was removed.

Figure 4: Extrapolation of DFS for alectinib and chemotherapy with and without the treatment waning and cure assumptions

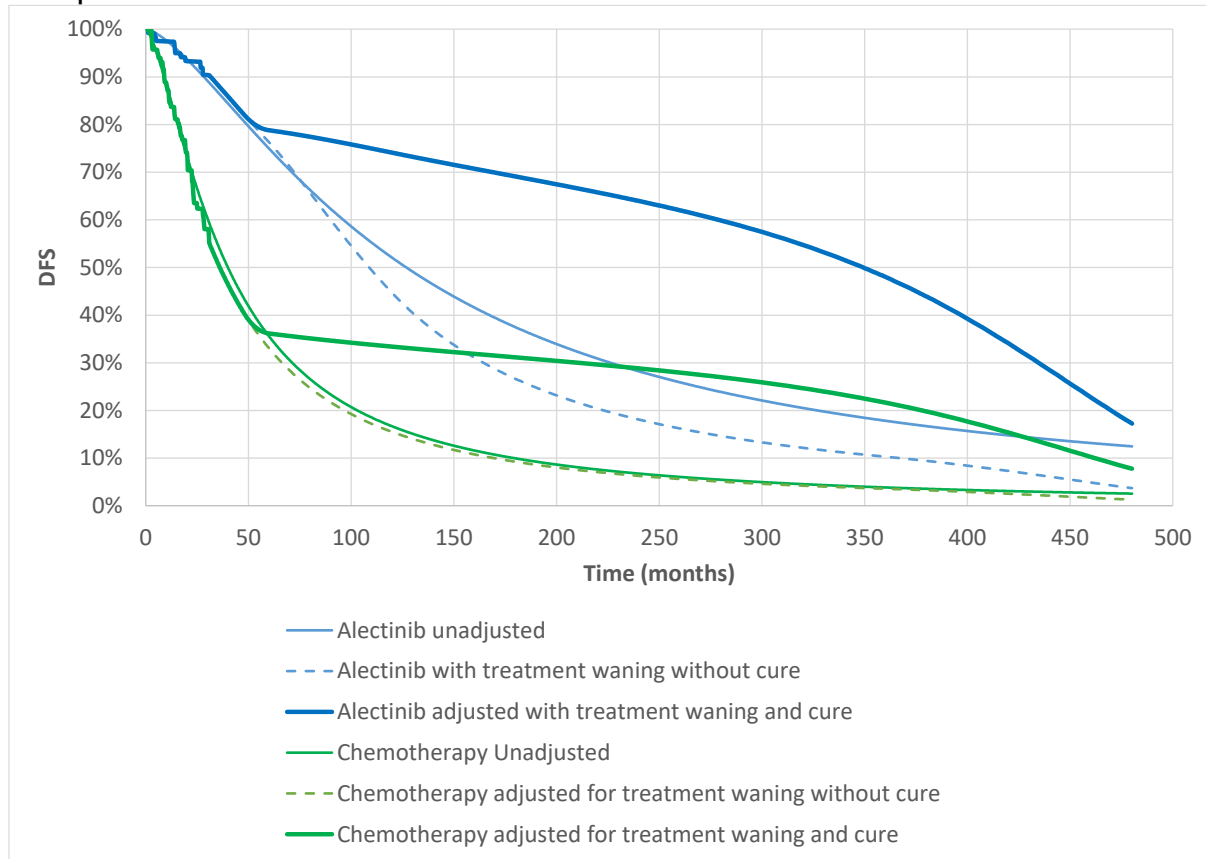


Figure compiled during this evaluation from data in worksheets “Alectinib” and “Chemo” in the economic model. DFS = disease-free survival

- 6.49 In the atezolizumab submission an adjustment for time limited treatment effect was applied to the economic model by assuming that the treatment effect of atezolizumab over BSC decreased linearly between Year 5 and Year 10. An adjustment for sustained DFS was applied by assuming that the proportion of ‘cured’ patients (i.e. no disease recurrence) increased linearly from Year 2 to a maximum of 91.5% in Year 5 (para. 7.7, atezolizumab, PSD, July 2022 PBAC meeting). The PBAC considered the assumptions regarding the proportion of patients achieving sustained DFS (i.e., ‘cured’) were not well justified in the submission. (para 7.7, atezolizumab, PSD, July 2022 PBAC meeting).
- 6.50 In the osimertinib submission, it was assumed that the proportion of patients cured in both treatment arms increased linearly from Year 4 (from 0%) to a maximum cure rate of 92% by Year 5 (i.e., transition to cure period = 1 year (Table 9, osimertinib PSD, November 2023 PBAC meeting). In the osimertinib submission, the “PBAC considered assuming a cure from Year 5 with the maximum cure at Year 7, which resulted in an absolute difference in the proportion of patients developing distant recurrence of 11% was more reasonable in the context of the remaining uncertainties associated with

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the durability of the DFS response” (para. 7.10, osimertinib, PSD, November 2023 PBAC meeting).

- 6.51 In the UK, NICE (National Institute for Health and Care and Excellence) recently (November 2024) published guidance³¹ on the assessment of alectinib in the same patient population as the current assessment for the PBAC. In the submission to NICE, it was assumed that a fixed proportion of patients would be considered cured at the 10-year timepoint, after which patients would experience no disease progression, and would only experience background rates of mortality (p96 NICE Committee Papers, Expert Assessment Group, EAG). The proportion of patients experiencing a cure was based on the mean of the most likely cure proportion estimates at the 10-year timepoint provided by clinicians. The EAG considered that the application of a cure assumption was broadly appropriate; the inclusion of a cure assumption was validated by the EAG’s clinical experts, and the methodology used was aligned with previous NICE appraisals (p105 NICE Committee Papers, EAG). Since comparison of ICERs suggested that this was a conservative assumption compared to a cure timepoint of 5 years, the EAG considered this approach to be acceptable. The judgement of the NICE committee regarding the assumption of a cure was not available on the NICE website. However, the EAG’s preferred cure proportion was 91% at 10 years based on the mean of clinicians’ responses from the company’s advisory board pooled across both treatments (p106, NICE Committee Papers, EAG).
- 6.52 In summary, there was very little relevant evidence regarding an appropriate assumption for modelling a cure proportion for the current assessment. The evaluation suggested applying the cure estimate from UK clinicians using a modified structured expert elicitation method, as reported by NICE, may be a better estimate as it related to the same patient population as the current submission. Applying a cure rate of 91% at 10 years increased the ICER from \$25,000 to < \$35,000 to \$45,000 to < \$55,000 per QALY gained.
- 6.53 The ESC advised that the NICE example was very conservative and that from a clinical perspective, a patient may be considered cured if disease-free at 5 years after ceasing active treatment. This aligned with previous PBAC consideration for osimertinib (paragraph 7.10, osimertinib, PSD, November 2023 PBAC meeting), which also factored in the absolute difference in the proportion of patients developing distant recurrence over a time horizon of 15 years. The ESC noted that the alectinib submission assumption of 92% cure rate at 5 years may be reasonable, however OS may have been overestimated, as the OS curves did not converge over the time horizon see Figure 4).

³¹ NICE (2024) Alectinib for adjuvant treatment of ALK-positive non-small-cell lung cancer Technology appraisal guidance TA1014 Published: 13 November 2024 <https://www.nice.org.uk/guidance/ta1014/evidence>

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- 6.54 The submission did not vary the utilities by age. This was not appropriate, especially for patients who are considered “cured”. When the utilities are adjusted for age, the ICER would increase. The PSCR provided a revised modelled economic evaluation incorporating time-dependent utility values as suggested by the evaluator, resulting in an increase in the ICER from \$25,000 to < \$35,000 to \$35,000 to < \$45,000 per QALY gained.
- 6.55 The utility in DFS off-treatment was estimated as 0.861 in the alectinib arm and 0.847 in the chemotherapy arm, based on the ALINA trial. The ESC noted treatment dependent utilities were applied in both the on-treatment and off-treatment health states and considered that the application of different utilities when patients are off-treatment was not appropriate. It was noted NICE also considered the same utility appropriate for both arms when off-treatment. When the average value of 0.854 was used in both treatment arms, the ICER increased marginally from \$25,000 to < \$35,000 to \$25,000 to < \$35,000 per QALY gained.
- 6.56 The ICER was sensitive to the costs in the first-line distant recurrence health state. Setting these costs to \$0, the ICER increased from \$25,000 to < \$35,000 to \$35,000 to < \$45,000 per QALY gained.
- 6.57 In the chemotherapy arm, patients who experience distant recurrence and who were ALK-positive would be expected to be treated with alectinib, which currently has dominant market share in the advanced or metastatic setting. This was consistent with international guideline recommendations (NCCN, 2024;³² NICE, 2024³³) and it was recommended that treatment with alectinib continue until disease progression occurs. Therefore, a treatment duration of 28.1 months for alectinib in 1L DR was applied in the economic model as per the median duration of alectinib treatment in the ALEX trial (Mok et al. 2020³⁴). This data source was appropriate. However, it was more appropriate to apply the mean treatment duration for the economic model. With the most parsimonious assumption that this follows an exponential function, the mean equals the median / $\ln(2)$ = 40.5 months. In this case, the ICER decreased from \$25,000 to < \$35,000 to \$25,000 to < \$35,000 per QALY gained.
- 6.58 It was recommended that lorlatinib treatment continues until disease progression occurs. The submission stated that a treatment duration of 57.0 months for lorlatinib in 1L DR was applied in the economic model as per the median duration of lorlatinib treatment in the CROWN study (Solomon et al. 2024).³⁵ The mean treatment duration

³² NCCN. (2024) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Non-Small Cell Lung Cancer. (Version 5.2024).

³³ NICE. (2024) National Institute for Health and Care Excellence (NICE). Lung cancer: diagnosis and management. NICE guidelines published 28 March 2019. Last updated 8 March 2024. Available from: www.nice.org.uk/guidance/ng122.

³⁴ Mok T, Camidge DR, Gadgeel SM, et al. (2020) Updated overall survival and final progression-free survival data for patients with treatment-naive advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Ann Oncol* 31: 1056-1064

³⁵ Solomon BJ, et al. (2024) Lorlatinib Versus Crizotinib in Patients With Advanced ALK-Positive Non-Small Cell Lung Cancer: 5-Year Outcomes From the Phase III CROWN Study. *J Clin Oncol* Vol 42, Issue 29: 3400-3409.

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was then estimated as $57.0 / \ln(2) = 82.2$ months, as above using the ratio of mean to median treatment durations.

- 6.59 The submission estimated the effective prices of lorlatinib and brigatinib and used these in the economic model.
- 6.60 The ICER was moderately sensitive to the costs in the second-line distant recurrence health state. Setting these costs to \$0, the ICER increased from \$25,000 to < \$35,000 to \$35,000 to < \$45,000 per QALY gained.
- 6.61 In the chemotherapy arm, it was expected that a patient with 2L DR would receive lorlatinib or alectinib again. However, for simplicity only lorlatinib was applied in the economic evaluation presented. As per the lorlatinib PSD, the median PFS (8.0 months) from Study 1001 was used as a proxy for the treatment duration for second- and subsequent-line lorlatinib therapy (Table 10, p14, lorlatinib, PSD, PBAC July 2021 meeting). This data source was reasonable. However, it was more appropriate to apply the mean treatment duration for the economic model. With the most parsimonious assumption that this follows an exponential function, the mean was the median / $\ln(2) = 11.5$ months. In this case, the ICER decreased from \$25,000 to < \$35,000 to \$25,000 to < \$35,000 per QALY gained.
- 6.62 By comparison, patients in the adjuvant alectinib treatment arm that had 2L DR, were assumed to be treated with brigatinib or alectinib. However, for simplicity only brigatinib was applied in the economic evaluation presented. It is unlikely that patients would be treated with brigatinib, because this would represent a third drug in the same class. Patients are more likely to receive chemotherapy. A median treatment duration of 34.9 months for brigatinib, derived from the ALTA-1L trial, was applied in the economic evaluation (p24 & p26, brigatinib, PSD, PBAC November 2019 meeting). The mean duration of brigatinib treatment was 50.4 months.
- 6.63 End of life care costs associated with lung cancer were estimated using participants in the Sax Institute's 45 and Up Study, which was a longitudinal study of 267,153 people aged ≥ 45 years in New South Wales (Goldsbury et al. 2020).³⁶ The average monthly cost at the end of life of \$6,409 was applied in the economic evaluation for both arms at the time at which patients die. However, it was more appropriate to add the costs in the final 6 months of life, which gives a total of \$38,454. This value was a slight over-estimate given that a relatively small proportion of total costs from Goldsbury et al. (2020) included PBS costs. Hence there may be some double counting of costs as the model also assumed costs of targeted PBS pharmaceutical treatment in 1L DR and 2L DR (Figure 4, Goldsbury et al. 2020). However, by far the greatest source of costs in Goldsbury et al. (2020) related to hospital-based care (Figure 4, Goldsbury et al. 2020).

³⁶ Goldsbury DE, Weber MF, Yap S, et al. (2020) Health services costs for lung cancer care in Australia: Estimates from the 45 and Up Study. *PLoS One* 15: e0238018.

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With the change of using the total cost for end of life of \$38,454, the ICER decreased from \$25,000 to < \$35,000 to \$25,000 to < \$35,000 per QALY gained.

6.64 Table 8 gives the key drivers of the model.

Table 8: Key drivers of the model

| Description | Method/Value | Impact |
|--|--|--|
| | | Base case: \$█ ¹ /QALY gained |
| Time horizon | Assumed 20 years. | High, favours alectinib. Assuming a time horizon of 15 years, for consistency with the recent submissions for atezolizumab (July 2022 PBAC meeting) and osimertinib (November 2023 PBAC meeting), increased the ICER to \$█ ² per QALY gained. |
| Transition probabilities of LRR to death | The weekly rate of 0.0046 for the chemotherapy arm was taken from Nakamichi et al (2017), and a higher weekly rate of 0.111 for the alectinib arm was taken from the ALEX trial. | High, favours alectinib. In the ALEX trial, patients received alectinib. This was not appropriate for estimating the transitions from LRR, as it was assumed that patients in this health state received either chemotherapy or radiotherapy. Applying both transition probabilities from Nakamichi et al (2017) increased the ICER from \$█ ¹ to \$█ ² per QALY gained. |
| Cure rate | The submission applied a cure rate that began at Year 4 and increased linearly to a maximum of 92% at Year 5 for patients in the DFS health state. | High, favours alectinib. Assuming a cure rate of 91% at 10 years (as per recent NICE appraisal of alectinib) increased the ICER to \$█ ³ per QALY gained. |
| Treatment duration in 1L DR and 2L DR | Submission assumed median durations in the model. | High, favours chemotherapy. Assuming mean treatment durations and correcting the source for 2 treatment duration values, the ICER decreased to \$█ ¹ per QALY gained. |

Source: Table 3.2, p58, Section 2.1.1.43, p89, Section 3.4.1, p67, p73, Section 2.1.1.37, p75, Section 2.1.1.43, p90 of the submission. DFS = disease-free survival, ICER = incremental cost-effectiveness ratio, LRR = locoregional recurrence, NICE = National Institute for Health and Care Excellence, QALY = quality-adjusted life years, 1L DR = 1st line distant recurrence, 2L DR = 2nd line distant recurrence
 The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000
² \$35,000 to < \$45,000
³ \$45,000 to < \$55,000

6.65 Table 9 presents the results of the stepped economic evaluation. The ICER fell substantially when extrapolating outcomes to 20 years and when applying the cure adjustment to DFS.

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Table 9: Results of the stepped economic evaluation

| Step and component | Alectinib | Chemotherapy | Increment |
|--|-----------|--------------|------------------|
| Step 1: trial-based costs and outcomes | | | |
| Costs (discounted) | \$█ | \$47,044 | \$█ |
| LYG (discounted) | 2.408 | 2.334 | 0.074 |
| Incremental cost/extra LYG gained | | | \$█ ¹ |
| Step 2: time horizon extended to 20 years | | | |
| Costs (discounted) | \$█ | \$99,014 | \$█ |
| LYG (discounted) | 8.702 | 5.508 | 3.194 |
| Incremental cost/extra LYG gained | | | \$█ ² |
| Step 3: treatment effect starts to decrease at year 5 and ceases at year 10 | | | |
| Costs (discounted) | \$█ | \$99,014 | \$█ |
| LYG (discounted) | 8.096 | 5.508 | 2.588 |
| Incremental cost/extra LYG gained | | | \$█ ³ |
| Step 4: cure adjustment to the DFS curves | | | |
| Costs (discounted) | \$█ | \$77,926 | \$█ |
| LYG (discounted) | 10.452 | 6.713 | 3.739 |
| Incremental cost/extra LYG gained | | | \$█ ⁴ |
| Step 5: Inclusion of medical resource use costs | | | |
| Costs (discounted) | \$█ | \$98,572 | \$█ |
| LYG (discounted) | 10.452 | 6.713 | 3.739 |
| Incremental cost/extra LYG gained | | | \$█ ⁴ |
| Step 6: Inclusion of AE costs | | | |
| Costs (discounted) | \$█ | \$99,850 | \$█ |
| LYG (discounted) | 10.452 | 6.713 | 3.739 |
| Incremental cost/extra LYG gained | | | \$█ ⁴ |
| Step 7: Inclusion of end-of-life costs | | | |
| Costs (discounted) | \$█ | \$103,599 | \$█ |
| LYG (discounted) | 10.452 | 6.713 | 3.739 |
| Incremental cost/extra LYG gained | | | \$█ ⁴ |
| Step 8: Inclusion of utilities | | | |
| Costs (discounted) | \$█ | \$103,599 | \$█ |
| QALYs (discounted) | 8.883 | 5.511 | 3.373 |
| Incremental cost/extra QALY gained (base case) | | | \$█ ⁴ |

Source: Based on Table 3.18, p94, Table 3.19, p95, Table 3.20, p95, Table 3.21, p96, Table 3.22, p96, Table 3.23, p97, Table 3.24, p97 of the submission and the economic model, worksheet "Results".

AE = adverse event, DFS = disease-free survival, LYG = life years gained, QALY = quality-adjusted life-year.

The redacted values correspond to the following ranges:

¹ > \$1,055,000

² \$35,000 to < \$45,000

³ \$45,000 to < \$55,000

⁴ \$25,000 to < \$35,000

6.66 Table 10 summarises the results of key univariate and multivariate sensitivity analyses.

6.67 The evaluation suggested an analysis with the following preferred assumptions implemented concurrently, resulting in an ICER of \$45,000 to < \$55,000 per QALY gained:

- 15-year time horizon; and
- 91% patients cured at Year 10; and
- Utility in DFS off-treatment set to 0.854 for both treatment arms; and

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- Treatment durations using mean values and correcting source of 2 treatment durations: for alectinib treatment arm: 1L DR lorlatinib and 2L DR brigatinib and
- End of life cost summed over 6 months and
- Weekly probability of transitioning from LRR to death in alectinib arm changed from 0.111 to 0.0046.

When updated with age adjusted utilities (as presented in PSCR model), the ICER would increase to \$75,000 to < \$95,000 per QALY gained.

Table 10: Results of the sensitivity analyses

| Analyses | Incremental cost | Incremental QALY | ICER | % change to ICER |
|---|------------------|------------------|-----------------|------------------|
| Base case | \$ [REDACTED] | 3.373 | \$ [REDACTED] 1 | |
| Discount rate (base case 5% costs and outcomes) changed to: | | | | |
| • 0% costs and outcomes | \$ [REDACTED] | 5.599 | \$ [REDACTED] 2 | [REDACTED] % |
| • 3.5% costs and outcomes | \$ [REDACTED] | 3.894 | \$ [REDACTED] 1 | [REDACTED] % |
| a. Time horizon (base case 20 years) changed to 15 years | \$ [REDACTED] | 2.674 | \$ [REDACTED] 3 | [REDACTED] % |
| b. Cure assumption (base case from Year 4, increasing linearly to a maximum of 92% at Year 5 in the DFS health state) changed to 91% patients cured at Year 10. | \$ [REDACTED] | 2.714 | \$ [REDACTED] 4 | [REDACTED] % |
| c. Utilities in DFS off-treatment (base case 0.861 in the alectinib arm and 0.847 in the chemotherapy arm) changed to average value of 0.854 used in both arms | \$ [REDACTED] | 3.275 | \$ [REDACTED] 1 | [REDACTED] % |
| d. Treatment durations (base case used median values) changed to estimated mean treatment durations for chemotherapy arm: 1L alectinib treatment, 2L lorlatinib treatment, alectinib arm: 1L lorlatinib treatment, 2L brigatinib treatment. Also correcting source for treatment duration for alectinib 1L lorlatinib and alectinib arm 2L brigatinib.* | \$ [REDACTED] | 3.373 | \$ [REDACTED] 2 | [REDACTED] % |
| e. End of life costs (base case used average monthly cost from 45 and Up Study = \$6,409) changed to sum of costs in the final 6 months of life = \$38,454. | \$ [REDACTED] | 3.373 | \$ [REDACTED] 1 | [REDACTED] % |
| f. Weekly probability of transition from LRR to death in alectinib arm (base case 0.111) changed to 0.0046 ¹ . | \$ [REDACTED] | 3.548 | \$ [REDACTED] 3 | [REDACTED] % |
| Multivariate analyses | | | | |
| a.b. 15-year time horizon and 91% patients cured at Year 10. | \$ [REDACTED] | 2.219 | \$ [REDACTED] 5 | [REDACTED] % |
| a.b.c. 15-year time horizon and 91% patients cured at Year 10 and utility in DFS off-treatment set to 0.854. | \$ [REDACTED] | 2.151 | \$ [REDACTED] 5 | [REDACTED] % |
| a.b.c.d. 15-year time horizon and 91% patients cured at Year 10 and utility in DFS off-treatment set to 0.854 and treatment durations using mean values and correcting source of 2 treatment durations. | \$ [REDACTED] | 2.151 | \$ [REDACTED] 3 | [REDACTED] % |
| a.b.c.d.e. 15-year time horizon and 91% patients cured at Year 10 and Treatment durations using mean values and correcting source of 2 treatment durations and end of life cost summed over 6 months. | \$ [REDACTED] | 2.151 | \$ [REDACTED] 1 | [REDACTED] % |
| a.b.c.d.e.f. 15-year time horizon and 91% patients cured at Year 10 and treatment durations using mean values and correcting source of 2 treatment durations and end of life cost summed over 6 months and changing weekly probability of transition from LRR to death in alectinib arm to 0.0046. | \$ [REDACTED] | 2.483 | \$ [REDACTED] 4 | [REDACTED] % |

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Source: Table 3.26, p100 of the submission. *Sensitivity analyses performed in this evaluation are shown in italics.*

1L = 1st line, 2L = 2nd line, DFS = disease-free survival, ICER = incremental cost-effectiveness ratio, LRR = locoregional recurrence, QALY = quality-adjusted life-year.

¹ cell C27, worksheet "Transition Inputs".

**note revised mean durations would increase this ICER to \$25,000 to < \$35,000 per QALY gained. Multi variate analyses in Table 8 using sensitivity analysis d. have not been revised.*

The redacted values correspond to the following ranges:

¹ \$25,000 to < \$35,000

² \$15,000 to < \$25,000

³ \$35,000 to < \$45,000

⁴ \$45,000 to < \$55,000

⁵ \$55,000 to < \$75,000

6.68 The ESC noted the PSCR provided a revised ICER with time-dependent utilities, as suggested by the evaluation (paragraph 6.54), with a revised base case of \$35,000 to < \$45,000 per QALY gained. The ESC considered the model should be further updated to reflect a number of other factors, to provide the PBAC with an alternative base case for consideration. The ESC advised the following assumptions should be considered in a multivariate sensitivity analysis, resulting in an ICER of \$45,000 to < \$55,000 per QALY:

- 15-year time horizon
- 92% patients cured at Year 5 in DFS health state (no change from submission base case)
- age adjusted utilities (as presented in PSCR model)
- equalised utilities post-treatment (utility in DFS off-treatment set to 0.854 for both treatment arms)
- Treatment durations using mean values (updated with correct sources of 2 treatment durations, noted in PSCR)
- sources of data for the transition probabilities of locoregional recurrence (LRR) to death aligned (weekly probability of transitioning from LRR to death in alectinib arm changed from 0.111 to 0.0046).

6.69 The ESC noted that, based on the MVSA described in paragraph 6.61, the mean undiscounted life years difference was 4.73 years (mean undiscounted life years for alectinib = 12.38; mean undiscounted life years for chemotherapy = 7.66), which seems large for a time horizon of 15 years. The ESC noted that the modelled OS curves do not converge over this time horizon, which is likely to have contributed to the large survival increment. The PBAC may wish to consider whether no convergence and an undiscounted incremental survival of 4.73 years over 15 years is clinically plausible, given the immature OS data. The Pre-PBAC Response stated it was more appropriate to refer to the mean discounted life years difference. The response noted that the equivalent mean discounted life years difference was 3.17 years (mean discounted life years for alectinib is 9.22 and for chemotherapy is 6.05) over a time horizon of 15 years. The Pre-PBAC Response further noted that the ESC and the PBAC have

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previously supported findings from the Sia 2023 report that PFS and DFS were possible surrogates for OS in adjuvant lung cancer.

6.70 The ESC noted the PBAC had previously considered osimertinib would be cost effective in the adjuvant treatment setting with a price reduction to maintain an ICER of \$35,000 to < \$45,000 per QALY (paragraph 7.10, osimertinib, PSD, November 2023 PBAC meeting). The pre-PBAC response noted that despite disagreement with the revised model assumptions proposed by the ESC, multi-sensitivity analyses of these assumptions together with an appropriate update of the end-of-life cost to \$38,454 results in an ICER of \$35,000 to < \$45,000/QALY gained. It further noted that the inclusion of model time horizons of 20 years (PBAC submission base case) and 40 years (NICE submission base case), results in an ICER of \$25,000 to < \$35,000/QALY and \$15,000 to < \$25,000/QALY, respectively. It was noted that this ICER did not use DPMQs and used assumed effective prices for other treatments in the locally advanced/metastatic setting.

Drug cost/patient/course

6.71 Table 11 presents the cost per patient per course of alectinib and chemotherapy. In the financial model, the estimated duration of chemotherapy treatment was incorrectly estimated as 23.9 months, the same as alectinib, rather than 4 cycles of 3 weeks per cycle (the table below presets the corrected value based on 4 cycles of 3 weeks per cycle). In the ALINA trial, a full course of treatment with alectinib lasted for 2 years, and a full course of chemotherapy involved 4 cycles of treatment each for 21 days.

Table 11: Drug cost per patient for alectinib versus chemotherapy

| | Alectinib Trial dose and duration | Alectinib Model | Alectinib Financial estimates | Chemotherapy Trial dose and duration | Chemotherapy Model | Chemotherapy Financial estimates |
|---------------------|--|-----------------|-------------------------------|--|--------------------|----------------------------------|
| Mean dose | 600 mg alectinib (4 x 150 mg capsules) administered orally twice daily | | | Cisplatin 75 mg/m ² with pemetrexed 500 mg/m ^{1.2} | | |
| Mean duration | 21.6 months | 21.5 months | 23.9 months | 2.0 months | | 2.0 months |
| Cost/patient/month | \$ | | | \$600 | | \$600 |
| Cost/patient/course | \$ | | | \$1,202 | | \$1,202 |

Source: Table 2.8, p32, Table 2.9, p32, Table 3.14, p85, of the submission “Drug Doses & Acquisition Costs” worksheet of the economic model.

Mg = milligram, m = metre.

¹ Patients in the control arm of the ALINA trial received one of the protocol-specified platinum-based chemotherapy regimens consisting of either cisplatin 75 mg/m² with pemetrexed 500 mg/m² or cisplatin 75 mg/m² with vinorelbine 25 mg/m², or cisplatin 75 mg/m² with gemcitabine 1250 mg/m² (p86 of the submission). In the ALINA trial, the most common chemotherapy regimen was platinum/pemetrexed (96 patients, 80%).

² 4 cycles of 3 weeks per cycle.

Estimated PBS usage & financial implications

6.72 This submission was not considered by DUSC.

6.73 The submission used an epidemiological approach to estimate the number of patients treated with alectinib. The key inputs for the financial estimates are given in Table 12.

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Table 12: Key inputs for financial estimates

| Data | Value | Source | Comment |
|---|--|--|--|
| Estimate the number of patients with the medical condition | | | |
| Estimation of incident cases of lung cancer | Yr 1: 15,368 Yr 2: 15,727 Yr 3: 16,080 Yr 4: 16,415 Yr 5: 16,736 Yr 6: 17,501 | AIHW Cancer data in Australia ³⁷ | The following amounts were found in the AIHW source. They were slightly higher than the submission values.: Yr 1: 15,685 Yr 2: 16,092 Yr 3: 16,497 Yr 4: 16,896 Yr 5: 17,250 Yr 6: 17,591 |
| Proportion of patients with NSCLC | 86.60% | Table 25, nivolumab, PSD, March 2023 PBAC meeting | The PBAC previously considered the value reasonable (Table 25, nivolumab, PSD, March 2023 PBAC meeting). |
| Proportion of patients with stage IB (tumours ≥4 cm) to IIIA NSCLC | 20.53% | Table 25, nivolumab PSD, March 2023 PBAC meeting | Reasonable and taken correctly from source PSD. |
| Proportion of patients with stage IB (tumours ≥4 cm) to IIIA NSCLC who receive surgical resection | 80.00% | Table 25, nivolumab, PSD, March 2023 PBAC meeting | The PBAC previously considered that the value appeared reasonable. However, no evidence to support this value was provided. Value was greater than those assumed in the atezolizumab (2022) (Table 20, atezolizumab, PSD, July 2022) and osimertinib (2023) submissions (Table 14, osimertinib, PSD, November 2023 PBAC meeting) (55.8% and 54.3% respectively). |
| Estimate the number of patients who would be eligible | | | |
| Proportion of resected stage IB (tumours ≥4 cm) to IIIA NSCLC with WHO PS ≤1 | 85.17% | Table 25, nivolumab, PSD, March 2023 PBAC meeting | The PBAC previously considered that this value was uncertain. 80% assumed in a sensitivity analysis in the current submission, the value preferred by the PBAC in the atezolizumab submission (Table 20, atezolizumab, PSD, July 2022 PBAC meeting). The PBAC considered this estimate was reasonable. |
| ALK positivity rate | 4.40% | Calendar year 2019 to 2023 MBS processed claims data for MBS items 73341 and 73337 | This figure was verified as consistent based other sources. ³⁸ However, the submission overestimated the ALK positivity rate. It would be preferable to use the number of positive cases from the ALK FISH confirmatory testing as the numerator in the calculation. The PBAC considered the estimate would be reasonable. |

³⁷ AIHW. (2023) Cancer data in Australia (CDIA). Cancer incidence projections (long-term). Accessed 12 June 2024 <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia/data>

³⁸ The first source was a retrospective chart review of patients with surgically resected stage I-III NSCLC (n=764), where an ALK positivity rate of 4% was reported based on FISH testing (Chaft et al 2018) (p112 of the submission). This was also consistent with Arbour & Riely (2017), who cited an ALK positive rate of approximately 5%.

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| Data | Value | Source | Comment |
|---|---|--|---|
| Estimate the number of patients likely to take alectinib | | | |
| Uptake rate of alectinib | Incident patients: █████% Grandfathered patients: █████% | Submission assumption | Uncertain but reasonable. |
| Estimate the utilisation and cost of treatments used within the budget impact analysis | | | |
| Treatment duration of alectinib | Median 23.9 months | CSR for ALINA trial 2023, Table 11, p49 | This was the median treatment duration. It would have been preferable to have used the mean duration of 21.3 months. |
| Treatment duration of cisplatin-pemetrexed | 4 cycles | CSR for ALINA trial 2023, Table 12, p50 | The submission erroneously applied a 23.9-month treatment duration for cisplatin-pemetrexed in the financial model. Chemotherapy had a maximum treatment duration of 4 cycles x 21 days per cycle = 2.8 months. In the ALINA trial, the mean duration of chemotherapy treatment was 2.0 months. Corrected estimates are provided in Table 13. <i>The PSCR included a revised financial model with this correction.</i> |
| DPMQ of alectinib | \$6,483.03 per pack of 224 tablets | PBS published price | Correct. |
| Weighted DPMA of cisplatin | \$147.25 per administration | Published ex-manufacturer price for PBS item 7224F and 4319H | Correct. |
| Weighted DPMA of pemetrexed | \$165.49 per administration | Published ex-manufacturer price for PBS item 7255W and 4600D | Correct. |
| MBS fee for parenteral administration of one or more antineoplastic agents | \$123.05 per administration | MBS item 13950 schedule fee | Correct. |

Source: Table 4.3, p110 of the submission. *Comments in italics from this evaluation. Evaluation comments in italics.*

AIHW = Australian Institute of Health and Welfare, ALK = anaplastic lymphoma kinase, CSR = Clinical study report, DPMA = dispensed price for maximum amount, DPMQ = Dispensed Price for Maximum Quantity, MBS=Medicare Benefit Schedule, NSCLC = non-small cell lung cancer, PBAC = Pharmaceutical Benefits Advisory Committee, PBS = Pharmaceutical Benefits Scheme; PSD = Public Summary Document, WHO = World Health Organisation.

6.74 The submission extracted the incidence of lung cancer given in Table 12 based on projections for lung cancer from the AIHW. The submission claimed that these projections were likely an underestimate since they do not consider the potential increase in incident patients with the introduction of a National Lung Cancer Screening Program starting 1 July 2025 (Australian Government, 2023)³⁹. The submission explored the potential impact of the National Lung Cancer Screening Program with a

³⁹ Australian Government. (2023) Establishing the National Lung Cancer Screening Program. Accessed 17 June 2024 <https://www.health.gov.au/our-work/nlcsp/establishing-program>

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sensitivity analysis. In this analysis, the proportion of patients with stage IB (tumours ≥ 4 cm) to IIIA NSCLC increased from 20.53% to 68%, reflecting the potential increase in early-stage NSCLC detected from a National Lung Cancer Screening Program. However, it seems unlikely that the introduction of the National Lung Cancer Screening Program will affect the number of incident patients or stage distribution, because most patients eligible for alectinib are non-smokers (ALK-positive NSCLC tends to occur in people with never or light smoking history compared with the general NSCLC population), whereas patients eligible for the National Lung Cancer Screening Program will be heavy smokers. Specifically, people will be eligible for the Program if they have a history of at least 30 pack-years of cigarette smoking and are still smoking or have a history of at least 30 pack-years of cigarette smoking and quit in the past 10 years.⁴⁰

- 6.75 The submission estimated the proportion of patients with stage IB (tumours ≥ 4 cm) to IIIA NSCLC who receive surgical resection as 80% taken from the nivolumab PSD (2023) (Table 25, nivolumab PSD, March 2023 PBAC meeting). This was verified as correct. However, no evidence was given to support this figure. Nonetheless, the PBAC considered this estimate to be reasonable (Table 25, nivolumab PSD, March 2023 PBAC meeting). This figure was substantially greater than the figure of 55.8% assumed in the recent atezolizumab submission (Table 20, atezolizumab PSD, July 2022 PBAC meeting). The atezolizumab figure was based on an IQVIA (2021) market research report and at that time the PBAC considered this figure reasonable. This value was used as a sensitivity analysis. The current submission value was also substantially greater than the figure of 54.30% assumed in the osimertinib submission (Table 14, osimertinib PSD, November 2023 PBAC meeting). In that submission, the PBAC considered this estimate to be reasonable and consistent with the figure from the atezolizumab submission. When the proportion of patients was decreased to 55.80%, the net financial impact of listing alectinib was reduced by approximately 30%. The PSCR argued the 55.8% resection rate in the adjuvant atezolizumab submission would be an underestimate for the proposed PBS population for alectinib, as it corresponds to a narrower population that excluded patients with stage IB NSCLC (PSD for atezolizumab 2022); however a sensitivity analysis using this lower estimate was included in the submission
- 6.76 The treatment duration of alectinib was assumed to be 23.9 months. This was the median duration in the ALINA trial, whereas it would have been preferable to assume the mean of 21.3 months in the ALINA trial. The treatment duration for chemotherapy was incorrectly assumed the same as for alectinib, 23.9 months. This was incorrect for treatment with chemotherapy, which had a maximum treatment duration of 4 cycles x 21 days per cycle = 2.8 months. In the ALINA trial, the mean duration of chemotherapy treatment was 2.0 months. The script volumes for years 2026 to 2030 were too high. The net cost to the government of listing alectinib was underestimated

⁴⁰ How the NLCSPP will work. Australian Government. <https://www.health.gov.au/our-work/nlcspp/how-it-works>

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by 1% over the period 2025-30. Corrected estimates are provided in Table 13. The PSCR included a revised financial model with this correction.

- 6.77 The submission estimated that [REDACTED] % of eligible patients would elect treatment with alectinib, given the significant DFS benefit from treatment. This was uncertain but the evaluation considered it may be reasonable.
- 6.78 The submission assumed that cisplatin and pemetrexed would be displaced by the listing of alectinib. In addition, other treatments would be displaced after the listing for alectinib. These include radiotherapy and chemotherapy in locoregional recurrence and brigatinib, alectinib and lorlatinib in distant recurrence, as per the economic analysis. If these treatments were included in the financial analysis, the net financial impact of listing alectinib would reduce because there would be less use of these subsequent treatments in the alectinib arm compared to the chemotherapy arm. The PSCR argued PBS listing of alectinib in the adjuvant setting should not preclude treatment with an ALK TKI (including lorlatinib, brigatinib, and alectinib) upon progression to locally advanced/metastatic NSCLC. However, ESC noted that the efficacy of adjuvant treatment with alectinib may result in reduced need for treatment in these late line settings and some savings may be expected.
- 6.79 The submission did not consider the costs of treating adverse events. When these costs were included in the analysis, the net cost to the PBS/RPBS reduced by approximately 0.5%.
- 6.80 Table 13 gives the estimated use and financial implications of listing alectinib.

Table 13: Estimated use and financial implications

| | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 | Year 6 |
|--|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Estimated extent of use | | | | | | |
| Number of patients treated | [REDACTED] ³ | [REDACTED] ³ | [REDACTED] ³ | [REDACTED] ³ | [REDACTED] ³ | [REDACTED] ³ |
| Number of scripts dispensed ¹ | [REDACTED] ⁴ | [REDACTED] ⁴ | [REDACTED] ⁴ | [REDACTED] ⁴ | [REDACTED] ⁴ | [REDACTED] ⁴ |
| Estimated financial implications of alectinib | | | | | | |
| Cost to PBS/RPBS less copayments | \$ [REDACTED] ⁵ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ |
| Estimated financial implications for chemotherapy | | | | | | |
| Cost to PBS/RPBS less copayments | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ |
| Net financial implications | | | | | | |
| Net cost to PBS/RPBS | \$ [REDACTED] ⁵ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ |
| Net cost to MBS | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ | -\$ [REDACTED] ⁷ |
| Net cost to PBS/RPBS/MBS ² | \$ [REDACTED] ⁵ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ | \$ [REDACTED] ⁶ |

Source: Table 4.9, p114, Table 4.10, p114, Table 14, p116, Table 19, p119, Table 20, p120, Table 4.24, p122, Table 4.25, p122 of the submission.

MBS=Medicare Benefit Schedule, PBS = Pharmaceutical Benefits Scheme, RPBS = Repatriation Pharmaceutical Benefits Scheme.

¹ Each patient had a mean of 23.5 scripts of alectinib.

² Figures in italics after correction of treatment duration of chemotherapy.

The redacted values correspond to the following ranges:

³ < 500

⁴ 500 to < 5,000

⁵ \$0 to < \$10 million

⁶ \$10 million to < \$20 million

⁷ net cost saving

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- 6.81 The total cost to the PBS/RPBS of listing alectinib was estimated to be \$10 million to < \$20 million in Year 6, and a total of \$70 million to < \$80 million in the first 6 years of listing.
- 6.82 The submission stated that a patient access program for alectinib was planned to commence following TGA approval of alectinib. Eligibility for the access program will strictly align with the proposed PBS restriction for alectinib.
- 6.83 The submission estimated < 500 patients with resected ALK-positive NSCLC (tumours ≥ 4 cm or node positive) and a WHO PS ≤ 1 were expected to be on the access program by 1 January 2025 and be eligible for PBS-subsidised treatment should the PBAC recommend alectinib as proposed. The ESC requested the sponsor provide an update on the patient access program in its pre-PBAC response. The pre-PBAC response confirmed that a patient access program for alectinib was open, with eligibility aligned with the proposed PBS restriction for alectinib and further confirmed that there were currently patients on the access program who are privately paying for adjuvant treatment with alectinib.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of alectinib for treatment of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumours ≥ 4 cm or node positive) as adjuvant therapy after tumour resection. The PBAC was satisfied that alectinib provided, for some patients, a significant improvement in efficacy in terms of disease-free survival (DFS) over platinum-based chemotherapy but the effect on overall survival (OS) benefit remained uncertain. The PBAC considered there was a high clinical need for effective therapies in this uncommon NSCLC subtype. The PBAC considered alectinib would be cost effective at a lower price, using the revised model parameters from the pre-PBAC response, to achieve an ICER consistent with that presented in the submission.
- 7.2 The PBAC noted that there were no PBS-reimbursed targeted therapies for resected ALK positive NSCLC which is an uncommon subset of NSCLC that is more likely to occur in young, female nonsmokers, resulting in central nervous system (CNS) metastases in 50–60% of patients. The PBAC noted strong support from MOGA and positive endorsements from consumers and health professionals for early access to alectinib in the adjuvant setting, noting there was a high clinical need for effective therapies given the limited efficacy of platinum-based chemotherapy in this setting.
- 7.3 The PBAC advised the following with regards to the restriction criteria:
- Consistent with other high-cost adjuvant listings (e.g. osimertinib, immune checkpoint inhibitors), re-treatment in the metastatic setting should not be permitted, and furthermore use of adjuvant therapy would preclude use of any ALK TKI in the recurrent setting. The PBAC would like to increase patient access in

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these situations, but evidence was required to determine a cost-effective price in the re-treatment setting. This may include targeted use of TKIs to treat emerging resistance mutations. Data such as overall response rate and time on treatment would be informative, as well as expected number of patients and financial implications.

- A single restriction, rather than separate initial, continuing and grandfather criteria, consistent with osimertinib, was appropriate, as this would be simpler for prescribers and reduce clinician error.
- The submission's proposed use of simple stage criteria rather than the AJCC staging was acceptable.
- The secretariat's suggested inclusion of a timeframe for commencement of treatment within 26 weeks after surgical resection, consistent with osimertinib, was appropriate (noting the ALINA trial required randomisation within 12 weeks which was unlikely to be feasible in clinical practice).
- The maximum treatment duration in the adjuvant setting should be 24 months.

- 7.4 The PBAC considered the nominated comparator of platinum-based chemotherapy was reasonable.
- 7.5 The PBAC noted the submission was based on the ALINA trial, an ongoing global, multicentre, open-label, phase III randomised controlled trial (RCT) that investigated the efficacy and safety of alectinib compared with platinum-based chemotherapy as adjuvant treatment in participants with resected ALK-positive stage IB (tumours ≥ 4 cm) to IIIA NSCLC (as classified according to the 7th edition of the Cancer Staging Manual of the AJCC/UICC).
- 7.6 The PBAC considered that the claim of superior clinical effectiveness was well supported by the ALINA trial in terms of a clinically meaningful benefit for DFS [HR 0.24 (95%CI: 0.13, 0.43)] with more patients not relapsed at 48 months in the alectinib arm (77%) compared to than the chemotherapy arm (46%). The PBAC noted that there was no signal of overall survival benefit at the prespecified DFS interim analysis with an event rate of 1.5% in the alectinib arm and 3.1% in the chemotherapy arm at the clinical cut-off date of a median 27.8 months. The PBAC were concerned that longer OS follow up may not establish an OS benefit given the availability of effective tyrosine kinase inhibitors (TKI) treatments post recurrence and requested that the committee be provided with mature OS data when available, to allow an opportunity to re-evaluate the cost-effectiveness of adjuvant alectinib. The PBAC also noted the SF-36v2 Mental Component Summary score at week 12 favoured alectinib in most domains.
- 7.7 The PBAC noted a higher rate of discontinuation in the chemotherapy arm compared to alectinib (12.5% versus 5.5% respectively). The PBAC noted the treatment duration of chemotherapy was shorter (median treatment for chemotherapy was 2.1 months compared to 23.9 months with alectinib) but was associated with more nausea (72.5% compared to 7.8%) whereas alectinib was associated higher rates liver function test

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dysfunction, myalgia, dysgeusia and oedema. The PBAC further noted that the proportion of participants who experienced at least one grade ≥ 3 adverse event was similar in the alectinib and chemotherapy arms (29.7 % and 30.1% respectively). The PBAC considered and that toxicity of alectinib was relatively low, but it will need to be managed earlier than with the current treatment algorithm where its use is reserved for the metastatic setting. Overall, the PBAC considered the claim of non-inferior (similar) safety to be reasonable, but did note that the impact of adverse events from adjuvant alectinib would typically be substantially prolonged compared to the adverse events from the comparator of adjuvant chemotherapy, due to the difference in planned treatment durations (2 years compared to 12 weeks).

- 7.8 The PBAC noted the submission presented a cost utility analysis based on the DFS outcomes of the ALINA trial with extrapolation to 20 years and a base case ICER of \$25,000 to < \$35,000 per QALY gained. The economic model applied 2 adjustments to the extrapolated DFS, including the limitation of treatment effect where the model allowed the treatment effect of alectinib to decrease over time and a cure adjustment where the model allowed patients to be considered cured (i.e. not experience recurrence or disease-related death) if they were disease-free for a certain number of years. The model assumed the treatment effect started to decrease at year 5 and ceased at year 10. The model applied a cure rate that began from Year 4 (i.e. 2 years after cessation of therapy) and increased linearly to a maximum of 92% at Year 5.
- 7.9 The PBAC agreed with the ESC that a 15-year time horizon was more appropriate given the precedents with atezolizumab and osimertinib and can be used to mitigate uncertainty in the estimated long-term costs and outcomes (see paragraph 6.40). The PBAC also agreed with the ESC that the cure assumption was reasonable, although the survival benefit may be overestimated (see paragraph 6.53).
- 7.10 The PBAC noted the ESC considered variation to a number of parameters to inform a revised base case (see paragraph 6.68). The PBAC noted the pre-PBAC response, despite disagreeing with the ESC's proposed changes to the model assumptions, accepted the ESC's suggested multi-sensitivity analysis together with an appropriate update of the end-of-life cost (see paragraph 6.69). The pre-PBAC response noted the resultant revised base case was within the range of an accepted ICER for osimertinib (\$35,000 to < \$45,000 per QALY gained).
- 7.11 The PBAC accepted the revised assumptions for the model as re-presented in the pre-PBAC response to include the appropriate end of life costs. The PBAC considered that although the cure assumption modelled was acceptable and consistent with osimertinib, modelled long-term benefits remained uncertain given immature survival data to support the modelled benefit and use of ALK-TKIs in the metastatic setting following adjuvant treatment, which was not adequately supported by the evidence. To further mitigate this uncertainty the PBAC considered alectinib would be cost effective in the adjuvant treatment setting with a price reduction to maintain an ICER in the order of \$25,000 to < \$35,000 per QALY gained, using the revised model from the pre-PBAC response with appropriate DPMQs rather than AEMPs.

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- 7.12 In regard to the estimated drug utilisation and financial implications, the PBAC noted that given these patients are likely to be younger and non-smokers, a high proportion would be eligible for surgical resection and the proposed estimate of 80% was reasonable. The PBAC agreed with the ESC that adjuvant use of alectinib may result in a reduced need for treatment in later line setting yet the potential cost savings were not accounted for in the analyses (see paragraph 6.78). The PBAC noted the median treatment duration of alectinib (23.9 months) was used, however the mean would be preferable (21.3 months), and the treatment duration for cisplatin should be updated to 2 months as it was incorrectly calculated as the same duration as alectinib (see paragraph 6.76). The PBAC considered the proposed alectinib uptake rates of ██████% in incident patients was uncertain but reasonable. The PBAC further noted that the number of grandfathered patients was not specified.
- 7.13 The PBAC noted that over 6 years the cost to the PBS/RPBS was estimated to be \$70 million to < \$80 million, and considered the financial impact was high despite the relatively small number of patients (approximately < 500 patients per year). The PBAC advised that a price reduction to achieve a cost effective ICER would need to be factored into the estimates.
- 7.14 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for alectinib:
- a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy (disease free survival), over placebo, on the basis of the ALINA trial;
 - b) The treatment is not expected to address a high and urgent unmet clinical need given alectinib is available in the metastatic treatment setting;
 - c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 7.15 The PBAC advised that alectinib should not be exempt from the Early Supply Rule as it currently applies to similar oral drugs for NSCLC.
- 7.16 The PBAC advised that alectinib is not suitable for prescribing by nurse practitioners.
- 7.17 The PBAC noted that this submission is not eligible for an Independent Review given it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Amend existing listing as follows:

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|---|---------------------|----------------------|----------------------|----------------|------------------|
| ALECTINIB | | | | | |
| alectinib 150 mg capsule, 4 x 56 | NEW | 1 | 224 | 3 | Alecensa |
| Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) | | | | | |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | | |
| Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment) - Telephone/Online PBS Authorities | | | | | |
| Administration advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
| Administrative Advice: No increase in the maximum quantity or number of units may be authorised. | | | | | |
| Administrative Advice: No increase in the maximum number of repeats may be authorised. | | | | | |
| Administrative Advice: Special Pricing Arrangements apply. | | | | | |
| Episodicity: Resected | | | | | |
| Severity: [blank] | | | | | |
| Condition: Non-small cell lung cancer (NSCLC) | | | | | |
| Restriction Summary / Treatment of Concept: | | | | | |
| Indication: Resected non-small cell lung cancer (NSCLC) | | | | | |
| Treatment Phase: Adjuvant therapy | | | | | |
| Clinical criteria: | | | | | |
| Patient must be both: (i) initiating treatment, (ii) untreated with an Anaplastic Lymphoma Kinase-Tyrosine Kinase Inhibitor (ALK-TKI) for non-small cell lung cancer; OR | | | | | |
| Patient must be continuing existing PBS-subsidised treatment with this drug; OR | | | | | |
| Patient must be both: (i) transitioning from existing non-PBS to PBS-subsidised supply of this drug, (ii) untreated with ALK-TKI at the time this drug was initiated. | | | | | |
| AND | | | | | |
| Clinical criteria | | | | | |
| The condition must be/have been at least one of: (i) node positive, (ii) at least 4 cm in size, | | | | | |
| AND | | | | | |
| Clinical criteria | | | | | |
| The treatment must be for the purpose of adjuvant therapy following surgical resection, | | | | | |
| AND | | | | | |
| Clinical criteria | | | | | |
| The treatment must be commenced within 26 weeks of surgery, | | | | | |
| AND | | | | | |
| Clinical criteria | | | | | |
| Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing, | | | | | |
| AND | | | | | |
| Clinical criteria | | | | | |

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| | Patient must have/have had a WHO performance status of no greater than 1 at treatment initiation with this drug, |
| | AND |
| | Clinical criteria |
| | The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition, |
| | AND |
| | Treatment criteria: |
| | Patient must be undergoing treatment that does not occur beyond the following, whichever comes first: (i) the first instance of disease progression/recurrence, (ii) 24 months of combined non-PBS and PBS-subsidised treatment for this condition from the first administered dose; mark any remaining repeat prescriptions with the words 'cancelled' where (i)/(ii) has occurred. |

8.2 The PBAC advised that it is not-appropriate to allow later line use of alectinib or an alternative ALK-TKI (crizotinib, ceritinib, brigatinib and lorlatinib) in the metastatic setting if patients have had alectinib in this early line.

8.3 The following amendments to the existing restriction are shown in italics and strikethrough.

Alectinib

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|---|------------------|-------------------|-------------------|----------------|------------------|
| ALECTINIB | | | | | |
| alectinib 150 mg capsule, 4 x 56 | 11226W | 1 | 224 | 3 | Alecensa |
| Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) | | | | | |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | | |
| Administration advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | |
| Administrative Advice: No increase in the maximum quantity or number of units may be authorised. | | | | | |
| Administrative Advice: No increase in the maximum number of repeats may be authorised. | | | | | |
| Administrative Advice: Special Pricing Arrangements apply. | | | | | |
| Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment) - Telephone/Online PBS Authorities | | | | | |
| Restriction Summary / Treatment of Concept: | | | | | |
| Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) | | | | | |
| Treatment Phase: Initial treatment | | | | | |
| Clinical criteria: | | | | | |
| <i>Patient must be untreated with an Anaplastic Lymphoma Kinase-Tyrosine Kinase Inhibitor (ALK-TKI) for NSCLC</i> | | | | | |
| AND | | | | | |
| Clinical criteria: | | | | | |
| The treatment must be as monotherapy <i>The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition</i> | | | | | |
| AND | | | | | |
| Clinical criteria: | | | | | |

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| | The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC |
| | AND |
| | Clinical criteria: |
| | Patient must have a WHO performance status of 2 or less |
| | AND |
| | Clinical criteria: |
| | Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing |
| Restriction Summary / Treatment of Concept: | |
| | Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) |
| | Treatment Phase: Continuing treatment |
| | Clinical criteria: |
| | The treatment must be as monotherapy The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition |
| | AND |
| | Clinical criteria: |
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition indication |
| | AND |
| | Clinical criteria: |
| | Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition |

Brigatinib

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|---|---|----------------|----------------|-------------|------------------|
| BRIGATINIB | | | | | |
| brigatinib 90 mg tablet [7] (& brigatinib 180 mg tablet [21], 1 pack | 11976H | 1 | 1 | 0 | Alunbrig |
| Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) | | | | | |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | | |
| | Administration advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | |
| | Caution: Careful monitoring of patients is required due to risk of developing pulmonary adverse events observed in patients within the first seven days of treatment with this drug. Patients must be instructed to report any new or worsening respiratory symptoms. | | | | |
| | Administrative Advice: No increase in the maximum quantity or number of units may be authorised. | | | | |
| | Administrative Advice: No increase in the maximum number of repeats may be authorised. | | | | |
| | Administrative Advice: Special Pricing Arrangements apply. | | | | |
| | Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment) - Telephone/Online PBS Authorities | | | | |
| Restriction Summary / Treatment of Concept: | | | | | |

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| | | | | | | |
|---|--|----------------------|-----------------------|-----------------------|--------------------|-------------------------|
| Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) | | | | | | |
| Treatment Phase: Initial treatment | | | | | | |
| Clinical criteria: | | | | | | |
| Patient must be untreated with an Anaplastic Lymphoma Kinase-Tyrosine Kinase Inhibitor (ALK-TKI) for NSCLC | | | | | | |
| AND | | | | | | |
| Clinical criteria: | | | | | | |
| The treatment must be as monotherapy The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition | | | | | | |
| AND | | | | | | |
| Clinical criteria: | | | | | | |
| The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC | | | | | | |
| AND | | | | | | |
| Clinical criteria: | | | | | | |
| Patient must have a WHO performance status of 2 or less | | | | | | |
| AND | | | | | | |
| Clinical criteria: | | | | | | |
| Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing | | | | | | |
| | | | | | | |
| MEDICINAL PRODUCT | | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
| medicinal product pack | | | | | | |
| BRIGATINIB | | | | | | |
| brigatinib 30 mg tablet, 28 | | 11980M | 4 | 112 | 3 | Alunbrig |
| brigatinib 90 mg tablet, 28 | | 11974F | 1 | 28 | 3 | Alunbrig |
| brigatinib 180 mg tablet, 28 | | 11984R | 1 | 28 | 3 | Alunbrig |
| | | | | | | |
| Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) | | | | | | |
| Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | | | |
| Administration advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. | | | | | | |
| Administrative Advice: No increase in the maximum quantity or number of units may be authorised. | | | | | | |
| Administrative Advice: No increase in the maximum number of repeats may be authorised. | | | | | | |
| Administrative Advice: Special Pricing Arrangements apply. | | | | | | |
| Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment) - Telephone/Online PBS Authorities | | | | | | |
| | | | | | | |
| Restriction Summary / Treatment of Concept: | | | | | | |
| Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) | | | | | | |
| Treatment Phase: Continuing treatment | | | | | | |
| Clinical criteria: | | | | | | |
| The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition | | | | | | |
| AND | | | | | | |
| Clinical criteria: | | | | | | |
| Patient must have previously received PBS-subsidised treatment with this drug for this condition indication | | | | | | |

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| | AND |
| | Clinical criteria: |
| | Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition |

Ceritinib

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|--|---|-------------------|-------------------|----------------|------------------|
| CERITINIB | | | | | |
| ceritinib 150 mg capsule, 3 x 50 | 11056X | 3 | 150 | 3 | Zykadia |
| | Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) | | | | |
| | Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | |
| | Administration 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> | | | | |
| | Administrative Advice: No increase in the maximum quantity or number of units may be authorised. | | | | |
| | Administrative Advice: No increase in the maximum number of repeats may be authorised. | | | | |
| | Administrative Advice: Special Pricing Arrangements apply. | | | | |
| | Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment) - Telephone/Online PBS Authorities | | | | |
| Restriction Summary / Treatment of Concept: | | | | | |
| | Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) | | | | |
| | Treatment Phase: Initial treatment | | | | |
| | Clinical criteria: | | | | |
| | <i>Patient must be untreated with an Anaplastic Lymphoma Kinase-Tyrosine Kinase Inhibitor (ALK-TKI) for NSCLC</i> | | | | |
| | AND | | | | |
| | Clinical criteria: | | | | |
| | <i>The treatment must be as monotherapy The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition</i> | | | | |
| | AND | | | | |
| | Clinical criteria: | | | | |
| | <i>The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC</i> | | | | |
| | AND | | | | |
| | Clinical criteria: | | | | |
| | <i>Patient must have a WHO performance status of 2 or less</i> | | | | |
| | AND | | | | |
| | Clinical criteria: | | | | |
| | <i>Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing</i> | | | | |
| Restriction Summary / Treatment of Concept: | | | | | |
| | Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) | | | | |
| | Treatment Phase: Continuing treatment | | | | |

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| | Clinical criteria: |
| | The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition |
| | AND |
| | Clinical criteria: |
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition |
| | AND |
| | Clinical criteria: |
| | Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition |

Crizotinib

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|--|--|-------------------|-------------------|----------------|------------------|
| CRIZOTINIB | | | | | |
| crizotinib 200 mg capsule, 60 | 10323H | 1 | 60 | 3 | Xalkori |
| | Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) | | | | |
| | Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners | | | | |
| | Administrative Advice: Special Pricing Arrangements apply. | | | | |
| | Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment) - Written/Online PBS Authorities | | | | |
| Restriction Summary / Treatment of Concept: | | | | | |
| | Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) | | | | |
| | Treatment Phase: Initial treatment | | | | |
| | Clinical criteria: | | | | |
| | Patient must be untreated with an Anaplastic Lymphoma Kinase-Tyrosine Kinase Inhibitor (ALK-TKI) for NSCLC | | | | |
| | AND | | | | |
| | Clinical criteria: | | | | |
| | The treatment must be as monotherapy The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition | | | | |
| | AND | | | | |
| | Clinical criteria: | | | | |
| | The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC | | | | |
| | AND | | | | |
| | Clinical criteria: | | | | |
| | Patient must have a WHO performance status of 2 or less | | | | |
| | AND | | | | |
| | Clinical criteria: | | | | |
| | Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing | | | | |

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| | <p>Prescribing Instructions: Applications for authorisation of initial treatment must be made via the Online PBS Authorities System (real time assessment) or in writing via HPOS form upload or mail. If the application is submitted through HPOS form upload or mail, it must include: (a) details of the proposed prescription; and (b) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).</p> |
| | <p>Prescribing Instructions: The following must be documented in the patient's medical records: (a) evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material.</p> |
| | <p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p> |
| Restriction Summary / Treatment of Concept: | |
| | Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) |
| | Treatment Phase: Continuing treatment |
| | Clinical criteria: The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition |
| | AND |
| | Clinical criteria: Patient must have previously received PBS-subsidised treatment with this drug for this condition <i>indication</i> |
| | AND |
| | Clinical criteria: Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition |
| | Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). |

Lorlatinib

| MEDICINAL PRODUCT medicinal product pack | PBS item code | Max. qty packs | Max. qty units | No. of Rpts | Available brands |
|---|------------------|-------------------|-------------------|----------------|------------------|
| LORLATINIB | | | | | |
| lorlatinib 25 mg tablet, 90 | 12096P | 1 | 90 | 3 | Lorviqua |
| lorlatinib 100 mg tablet, 30 | 12091J | 1 | 90 | 3 | Lorviqua |
| Category / Program: <input checked="" type="checkbox"/> GENERAL - General Schedule (Code GE) | | | | | |

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| | |
|--|---|
| | Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners |
| | Administration advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333. |
| | Administrative Advice: No increase in the maximum quantity or number of units may be authorised. |
| | Administrative Advice: No increase in the maximum number of repeats may be authorised. |
| | Administrative Advice: Special Pricing Arrangements apply. |
| | Restriction type: <input checked="" type="checkbox"/> Authority Required (immediate assessment) - Telephone/Online PBS Authorities |
| Restriction Summary / Treatment of Concept: | |
| | Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) |
| | Treatment Phase: Initial treatment |
| | Clinical criteria: |
| | <i>Patient must be untreated with an Anaplastic Lymphoma Kinase-Tyrosine Kinase Inhibitor (ALK-TKI) for NSCLC</i> |
| | AND |
| | Clinical criteria: |
| | The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication |
| | AND |
| | Clinical criteria: |
| | The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC |
| | AND |
| | Clinical criteria: |
| | Patient must have a WHO performance status of 2 or less |
| | AND |
| | Clinical criteria: |
| | Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as either: (i) 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH) testing, (ii) positive next generation sequencing (NGS) testing |
| Restriction Summary / Treatment of Concept: | |
| | Indication: Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC) |
| | Treatment Phase: Continuing treatment |
| | Clinical criteria: |
| | The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this PBS indication |
| | AND |
| | Clinical criteria: |
| | Patient must have previously received PBS-subsidised treatment with this drug for this condition <i>indication</i> |
| | AND |
| | Clinical criteria: |
| | Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition |

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

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

10 Sponsor's Comment

Roche welcomes the positive recommendation for PBS listing of alectinib as adjuvant treatment in patients following tumour resection of anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) (tumours ≥ 4 cm or node positive). However, Roche is disappointed by the PBAC's decision not to allow alectinib re-treatment in the locally advanced/metastatic setting, and a further limitation that adjuvant therapy with alectinib would preclude the use of any ALK tyrosine-kinase inhibitor (TKI) in the recurrent setting. Roche notes ALK-positive NSCLC is a distinct molecular subtype where disease progression often remains ALK-driven. Roche believes that continuing ALK inhibition, even after disease progression, can provide better disease control and improve quality of life outcomes. Roche notes there are three generations of ALK TKIs available and reimbursed on the PBS, each with different mechanisms of action targeting ALK-positive disease. Roche believes that there is well-established, high-quality evidence demonstrating the efficacy of targeted treatments in advanced ALK-positive NSCLC and seeks to further engage with the PBAC and the Department of Health, Disability and Ageing regarding re-treatment.