

7.04 MOBOCERTINIB, Capsule 40 mg, EXKIVITY[®], Takeda Pharmaceuticals Australia Pty Ltd.

1 Purpose of submission

- 1.1 The standard re-entry resubmission requested a General Schedule Authority Required listing for the treatment of adults with locally advanced (Stage IIIB/IIIC) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) harbouring epidermal growth factor receptor exon 20 insertion (*EGFR* ex20ins) mutations whose disease has progressed on or after platinum-based chemotherapy (PBC).
- 1.2 Listing was requested on the basis of a cost-utility analysis *versus* standard *EGFR* tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitor (ICI) monotherapy, and chemotherapy (henceforth referred to in this document as standard of care [SOC]), although the nominated comparator in the resubmission was chemotherapy. The PBAC previously considered that defining the comparator as SOC, comprising all treatments (standard *EGFR* TKIs, ICIs, and chemotherapy) was not appropriate, and that chemotherapy agents such as taxanes should be defined as the comparator (para 5.5 and 7.4, mobocertinib, public summary document (PSD), November 2022 PBAC meeting).
- 1.3 Key components addressed by the resubmission are presented in Table 1.

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

Component	Description
Population	Epidermal growth factor receptor exon 20 insertion (<i>EGFR</i> ex20ins) mutation-positive locally advanced (stage IIIB or stage IIIC) or metastatic (stage IV) non-small cell lung cancer (NSCLC) in patients whose disease has progressed on or after platinum-based chemotherapy (PBC).
Intervention	Mobocertinib (EXKIVITY [®]) 160 mg (4 X 40 mg capsules) once daily.
Comparator	Standard of care ^a
Outcomes	Progression-free survival (PFS), overall survival (OS), response rate (cORR)
Clinical claim	Mobocertinib is superior in terms of effectiveness compared with standard of care in patients with locally advanced or metastatic NSCLC and <i>EGFR</i> ex20ins mutations who have progressed on or following prior treatment with PBC. Mobocertinib is expected to have a different safety profile compared to chemotherapy or immunotherapy; its safety profile is acceptable and similar to that of other TKIs.

Source: Table ES.1, p1, Executive Summary of the resubmission.

TKIs=tyrosine kinase inhibitors.

^a The nominated comparator in Section 1 of the resubmission was chemotherapy. The term "SOC" in the remaining sections of this ESC Advice refers to all treatments (standard *EGFR* TKIs, ICIs, and chemotherapy). When discussing chemotherapy alone as the nominated comparator, the term "chemotherapy" is used.

Blue shading indicates information previously seen by the PBAC.

2 Background

Registration status

- 2.1 Mobocertinib (EXKIVITY) received provisional approval from the TGA on 19 July 2022 for “the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that has an exon 20 insertion mutation of the epidermal growth factor receptor (*EGFR*), who have received prior platinum-based chemotherapy”.
- 2.2 Conditions of provisional approval include the provision of all clinical study reports (CSRs) from Study TAK-788-3001 (interim and final) and other post-marketing safety studies. Study TAK-788-3001 is an ongoing randomised controlled trial (RCT) comparing the effectiveness of mobocertinib (TAK-788) as first-line treatment with PBC (pemetrexed/cisplatin or pemetrexed/carboplatin) in patients with locally advanced or metastatic NSCLC whose tumours have *EGFR* ex20ins mutations. The next data analysis is expected to be performed in 2023 (TGA Delegate’s Overview). The ESC noted that estimated study completion date for Study TAK-788-3001 is June 2026.*

Previous PBAC consideration

- 2.3 At the November 2022 PBAC meeting, mobocertinib was considered but not recommended by the PBAC for the treatment of adults with *EGFR* ex20ins positive locally advanced or metastatic NSCLC who have received PBC. The main PBAC concerns and how they were addressed in the resubmission are summarised in Table 2.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Population	The ESC and PBAC considered that it would be appropriate for patients to have WHO performance status of 2 or less, consistent with the current listings for <i>EGFR</i> TKIs (para 3.10, November 2022 PSD).	Addressed. The restrictions have been changed to allow use of mobocertinib treatment in patients with WHO performance status ≤ 2.
Comparator	The PBAC considered that the nominated comparator of SOC, comprising <i>EGFR</i> TKIs, ICI monotherapy, and chemotherapy, in the original submission was inappropriate as <i>EGFR</i> TKIs and ICI monotherapy are generally not used in the proposed target population. The PBAC nominated chemotherapy agents such as taxanes as the most appropriate comparator and the most likely second line treatment used in Australia (para 7.1 and 7.4, November 2022 PSD).	Partially addressed. The resubmission nominated chemotherapy as the comparator. However, chemotherapy was not limited to taxanes as only a few patients in the comparator studies (5002 and 5008) received taxanes (n=7). The entire chemotherapy cohort (N=23) from the comparator studies was used in the ITCs with mobocertinib.

* TAK-788 as First-Line Treatment Versus Platinum-Based Chemotherapy for Non-Small Cell Lung Cancer (NSCLC) With *EGFR* Exon 20 Insertion Mutations - Full Text View - ClinicalTrials.gov.
<https://clinicaltrials.gov/ct2/show/nct04129502>

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Component	Matter of concern	How the resubmission addresses it
Clinical evidence	The PBAC considered that the retrospective SOC studies (Study 5008 and Study 5002) have limited applicability, in terms of treatments administered (EGFR TKIs, ICI monotherapy, and non-PBC), to current clinical practice in Australia (para 7.5, November 2022 PSD).	Addressed. The resubmission presented an ITC of the mobocertinib cohort from Study 101 versus the pooled chemotherapy cohort from Studies 5002 and 5008.
	The ESC had substantial reservations about the applicability of both the comparator studies, given that neither study provided a pure effect of chemotherapy-based treatments for a group of patients with a similar treatment history to Study 101. It considered that a comparison of mobocertinib with pooled results from Studies 5008 and 5002 may be more reasonable than a comparison with either study alone (para 6.22, November 2022 PSD)	Addressed. In the resubmission, the ITC of mobocertinib versus chemotherapy used the pooled data from Studies 5002 and 5008.
	The PBAC considered that the evidence presented is associated with a very high degree of uncertainty that did not permit either a comparison of mobocertinib with the appropriate comparator (chemotherapy), or a comparison of safety (para 7.1, November 2022 PSD)	Partially addressed. An ITC of the mobocertinib cohort from Study 101 with a pooled chemotherapy cohort from Studies 5002 and 5008 was presented in the resubmission. However, given the major transitivity issues across treatment cohorts indirectly compared and the small sample size of the chemotherapy cohort (N=23), the incremental benefit of mobocertinib over chemotherapy remains uncertain. There is no comparative evidence of safety for mobocertinib versus chemotherapy, as safety data was not collected in the comparator studies.
Clinical effectiveness	The PBAC considered that the submission's claim of superior effectiveness was very uncertain, due to a high risk of bias and small sample sizes, and that inflating the populations (using the adjusted IPTW methodology) had the risk of exacerbating the potential biases (para 7.6, November 2022 PSD).	Not addressed. These concerns have not been resolved because there were numerous limitations associated with the IPTW-based ITCs of mobocertinib versus chemotherapy and versus SOC.
	The PBAC considered that the magnitude of a potential incremental benefit of mobocertinib compared with SOC was uncertain and may be overestimated by the inclusion of EGFR TKIs and ICI monotherapy that are not effective in the second line setting for the proposed indication and are not used in Australian clinical practice (para 7.6, November 2022 PSD).	Partially addressed. The resubmission presented the ITC of mobocertinib with chemotherapy. However, given the limitations associated with this ITC, the indirect estimates of the treatment benefit of mobocertinib in comparison with chemotherapy remain uncertain.
	The PBAC considered that the median OS for mobocertinib of 20.17 months in Study 101, compared to 9.76 months for SOC Study 5008 (adjusted IPTW HR = 0.42, p = 0.0025) was implausible, given the relatively low cORR of 28% for mobocertinib (para 7.6, November 2022 PSD).	Addressed The resubmission indicated that 78% of patients receiving mobocertinib in Study 101 achieved a CR, PR or SD ^a . The median OS was 32 months in the responders (CR and PR, 28%) and 20 months in patients with SD (50%).

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Component	Matter of concern	How the resubmission addresses it
Clinical harms	The original submission did not present a safety comparison of mobocertinib against SOC, and considered that mobocertinib may have a “different” safety profile that is not non-inferior to SOC (para 7.7, November 2022 PSD).	Not addressed. There is no comparative evidence of safety for mobocertinib. Safety data were not collected during the comparator studies.
Economic evaluation	PBAC considered that a comparison of mobocertinib with pooled results from studies 5008 and 5002 may be more reasonable than a comparison with either study alone (para 6.22, November 2022 PSD).	Addressed. The resubmission used pooled data from study 5002 and 5008 used in the analysis
	Agents currently used in Australian clinical practice in the second-line treatment setting for advanced NSCLC include docetaxel, gemcitabine, pemetrexed, carboplatin and paclitaxel. Defining chemotherapy as comparator/s was appropriate and would likely be taxane-based in the Australian context (para 5.2, November 2022 PSD).	Partially addressed KM data used in the resubmission remains unchanged and includes treatments not used in Australian clinical practice (immunotherapies and TKIs). KM data for chemotherapies alone are used in a sensitivity analysis.
	The half cycle correction (HCC) was applied to all costs and outcomes. As all patients initiate the treatment at the start of the cycle, HCC may not be required for the costs (para 6.51, November 2022 PSD).	Addressed. The half cycle correction to drug costs was removed from the model.
	PBAC considered that limiting the cost of SOC to chemotherapy regimens, which is more likely to be the treatment used in the absence of mobocertinib, may be a reasonable approach.	Addressed Costs in the resubmission were limited to chemotherapy regimens only.
	The PBAC noted it had previously recommended other targeted therapies for the second line treatment of NSCLC with ICERs of \$45,000 to \$75,000 per QALY gained. The PBAC considered that the resulting ICER of \$75,000 to < \$95,000 did not align with the prespecified base case proposed by the evaluation and remained unacceptably high (para 6.74, November 2022 PSD).	Addressed A ■■■% reduction to the price is proposed resulting in an incremental cost per QALY within the range requested by PBAC.
Financial estimates	The PBAC considered the financial estimates presented in the submission should present revised financial estimates consistent with the DUSC advice for: 1. The proportion of patients with Stage IIIB/IV NSCLC The DUSC noted that the financial analysis only included incident patients with Stage IIIB/IV disease at initial diagnosis; however, there will be some patients who are diagnosed with early stage NSCLC but subsequently progress to Stage IIIB/IV. These patients are also eligible for mobocertinib but not considered in the financial estimates.	Addressed. The resubmission also considered patients diagnosed at an earlier stage (Stage IIIA) who progress to Stage IIIB/IV. The resubmission identified 11.8% of NSCSLC patients to be at Stage IIIA. It was assumed that 60% of Stage IIIA patients will progress to Stage IIIB/IV.
	2. The prevalence of EGFR exon20ins	Addressed.

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Component	Matter of concern	How the resubmission addresses it
	The DUSC commented that financial estimates are sensitive to the estimate of the proportion of patients with ex20in EGFR disease and the assumption of 8% is at the higher end of values reported in the literature.	The resubmission identified the study by Moore 2018, which estimated the proportion of EGFR positive NSCLC patients with Exon 20 insertions (8.96%) based on next-generation sequencing technique.
	3. The number of prevalent patients The inclusion of prevalent NSCLC patients in the financial analysis is appropriate. However, the use of the incident cases in the first year of listing (not in the years before listing) and the survival after second-line SOC (not after first-line PBC) to determine the number of prevalent patients eligible for mobocertinib was not justified in the submission.	Addressed. The resubmission revised the number of prevalent patients to include incident cases in the years before listing and the time from diagnosis of advanced disease to initiation of 2L therapy. Based on Study 101, the resubmission assumed time from diagnosis of advanced disease to initiation of 2L therapy to be 1.31 years (15.7 months). Therefore, 100% of incident patients in 2023 and 31% of incident patients in 2022 are expected to be considered for 2L treatment with mobocertinib in year 2024.
	4. Estimated cost offsets to PBS/RPBS are likely to have been overestimated DUSC considered that the limited use of immunotherapies and EGFR TKIs in the current refractory setting for the proposed population likely over-estimated the cost offsets in the model.	Addressed. The resubmission limited the comparator therapies to chemotherapies alone. Therefore, the revised cost offsets in resubmission included regimens for mono chemotherapy docetaxel and pemetrexed or combination therapies of carboplatin with either gemcitabine, pemetrexed, or paclitaxel described in study 5002 and 5008.

Source: Mobocertinib November 2022 PSD; Mobocertinib resubmission.

cORR=confirmed objective response rate; CR=complete response; EGFR=epidermal growth factor receptor; ESC=Economics Sub Committee; HR=hazard ratio; ICI=immune checkpoint inhibitor; ITC=indirect treatment comparison; IPTW=inverse probability treatment weighting; OS=overall survival; PBAC=Pharmaceutical Benefits Advisory Committee; PR=partial response; PSD=public summary document; SD=stable disease; SOC=standard of care comprising all treatments (standard EGFR TKIs, ICIs and chemotherapy); TKI=tyrosine kinase inhibitor; WHO=World Health Organization.

^a Stable disease was defined as tumour reduction <30%.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty (DPMQ)	Max. qty packs	Max. qty units	Nº. of Rpts	Available brands
MOBOCERTINIB					
Mobocertinib, 40mg capsules	Published price: \$11,515.76 Effective price: \$█	1	112	5	EXKIVITY

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online application avenues)
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.
Indication: Stage IIIB or IIIC (locally advanced) or IV (metastatic) non-small cell lung cancer (NSCLC).
Treatment Phase: Initial PBS-subsidised treatment
Clinical criteria

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The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria
Patient must have/have had a WHO performance status of 2 or less prior to initiation of treatment with this drug for this condition.
AND
Clinical criteria
Patient must not have previously received this drug for this condition; OR
Patient must be each of: (i) currently receiving non-PBS subsidised supply for this drug for this PBS indication, (ii) untreated with this drug at the time that non-PBS subsidised supply was commenced, (iii) free of disease progression since commencing non-PBS subsidised supply
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 had progressive disease following platinum-based chemotherapy
AND
Clinical criteria
Patient must have evidence in tumour material of an activating epidermal growth factor receptor (<i>EGFR</i>) exon 20 insertion mutation
Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once. Following completion of the initial PBS-subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online application avenues)
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.
Indication: Stage IIIB or IIIC (locally advanced) or IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment Phase: Continuing
Clinical criteria
The treatment must be the sole PBS-subsidised therapy for this condition
AND
Clinical criteria
Patient must have previously received PBS-subsidised treatment this drug for this condition
AND
Clinical criteria
Patient must not have developed disease progression while receiving treatment with this drug for this condition
Administrative Advice: Special Pricing Arrangements apply.
Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

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Source: Table 1-1 p2 and Figure 1-1 pp3-5 of the resubmission.

Max=maximum; PBS=Pharmaceutical Benefits Schedule; Qty=quantity; Rpts=repeats; WHO=World Health Organisation.

Blue shading indicates information previously seen by the PBAC.

- 3.1 As in the original submission, the resubmission proposed a Special Pricing Arrangement. The effective ex-manufacturer price requested in the resubmission was % lower than that proposed in the previous submission (\$) vs. \$ per pack [112 capsules]).
- 3.2 The proposed restrictions in the resubmission incorporated all changes suggested by the PBAC/Secretariat at its November 2022 meeting, including:
- Use of the nomenclature “mutation” rather than “variant” (consistent with current PBS listings of other *EGFR* TKIs);
 - Defining locally advanced NSCLC as Stage IIIB and Stage IIIC (in line with the updated American Joint Committee on Cancer [AJCC] Cancer Staging 8th edition);
 - A World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2 prior to initiation of mobocertinib (consistent with the current listings for *EGFR* TKIs); and
 - Removing the grandfather restriction as the Secretariat’s suggested changes accommodated transitioning grandfathered patients to PBS funded treatment in the initial treatment phase restriction (para 3.4, 3.5 and 3.10, mobocertinib PSD, November 2022 PBAC meeting).
- 3.3 The November 2022 mobocertinib submission requested access be limited to non-squamous or not otherwise specified NSCLC subtypes. At that time, the PBAC agreed with the ESC that it may be appropriate to remove the reference to histology in the criteria to allow patients with squamous cell NSCLC to access treatment, due to the very small number of these patients in the community and their inclusion within the trial used as evidence in the submission. However, in November 2022 the PBAC noted that MBS item 73337 refers specifically to testing for *EGFR* status in non-squamous or ‘not otherwise specified’ histology and patients with squamous histology do not currently have access to testing (para 3.9, mobocertinib, PSD, November 2022 PBAC meeting). The ESC noted that MBS item 73337 may be superseded by the November 2022 Medical Services Advisory Committee (MSAC) recommendation for the creation of new MBS items for small next generation sequencing panels for biomarker testing of patients with NSCLC. As such, the ESC considered it may again be appropriate to remove the reference to histology in the criteria.

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

4 Population and disease

- 4.1 Lung cancer is the fourth most often diagnosed cancer for both men and women in Australia, representing approximately 9% of all new cancer diagnoses[†]. Advanced NSCLC is a life-threatening condition. Activating mutations of the *EGFR* oncogene occur in a subset of NSCLC and are associated with female sex, non-smoker status and adenocarcinoma histology[‡]. *EGFR* ex20ins are a rare subset of *EGFR* mutations for which there are no targeted therapies currently funded in Australia.
- 4.2 The proposed population for mobocertinib is *EGFR* ex20ins mutation-positive locally advanced (Stage IIIB or Stage IIIC) or metastatic (Stage IV) NSCLC in patients whose disease has progressed on or after PBC.
- 4.3 Mobocertinib is an oral, selective irreversible TKI with binding affinity to *EGFR* ex20ins variants at lower concentrations compared to wild-type *EGFR*. This differentiates it from available classical first-generation (gefitinib and erlotinib) and second-generation (afatinib) *EGFR* TKIs to which ex20ins variants are typically insensitive. For eligible patients with locally advanced or metastatic *EGFR* ex20ins positive NSCLC, mobocertinib would replace current therapies in the second-line NSCLC treatment setting, mainly chemotherapy.
- 4.4 Amivantamab (RYBREVA[®]) has provisional TGA approval for the same indication as mobocertinib but has a different mode of action (*EGFR*-directed and mesenchymal-epidermal transition (MET) receptor-directed TKI). The National Comprehensive Cancer Network (NCCN) guidelines[§] for NSCLC recommend that amivantamab can be used if patients have previously received mobocertinib and *vice versa*. Mobocertinib and amivantamab are not currently PBS listed.

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

5 Comparator

- 5.1 The resubmission nominated chemotherapy as the comparator.
- 5.2 The nominated comparator in the original submission was SOC comprising standard *EGFR* TKIs, ICIs, and chemotherapy. The PBAC previously noted that evidence in the literature and treatment guidelines does not support *EGFR* TKI therapy in the proposed patient population, and the PBAC agreed with the evaluation and the ESC that it is highly unlikely that TKIs are used routinely in this context in Australia.

[†] John T, Cooper WA, Wright G, Siva S, Solomon B, Marshall HM, et al. Lung Cancer in Australia. *Journal of Thoracic Oncology*. 2020;15(12):1809-14.

[‡] Leal JL, Alexander M, Itchins M, Wright GM, Kao S, Hughes BG, et al. *EGFR* Exon 20 Insertion Mutations: Clinicopathological Characteristics and Treatment Outcomes in Advanced Non-Small Cell Lung Cancer. *Clinical Lung Cancer*. 2021;22(6):e859-e69.

[§] National Comprehensive Cancer Network. NCCN clinical practice guidelines in Oncology (NCCN Guidelines[®]) non-small cell lung cancer Version 2.2023.

Similarly, the PBAC previously noted there is limited evidence of the benefit of ICI monotherapy in refractory *EGFR* ex20ins positive NSCLC, and most patients would be treated with ICIs in the first line setting and not receive them second line. The PBAC noted that chemotherapy agents, such as taxanes, are the most likely treatments used in Australia second line and that these agents are therefore the appropriate comparator for refractory *EGFR* ex20ins positive NSCLC (para 7.4, mobocertinib, PSD, November 2022 PBAC meeting). The Pre-Sub-Committee Response (PSCR) detailed the therapy received by patients (n=13) with a diagnosis of stage IIIB-IV *EGFR* ex20ins NSCLC initiated on PBC collected from the Victorian Lung Cancer Registry (VLCR). The PSCR noted that for the first PBC the majority of patients (10/13, 77%) did not receive an adjunctive ICI. Of the 15 therapies received after the first PBC, only 2 involved single agent chemotherapy, whereas 8 included an ICI, most commonly as monotherapy but also in combination with PBC and bevacizumab. The PSCR argued that the results indicate ICIs are used in both first and subsequent lines of therapy and therefore excluding them from consideration is a conservative view for this patient population. The ESC noted the retrospective cohort study from the VLCR was based on data on 13 patients treated in a single Australian state and as such considered it may have limited applicability. Furthermore, the ESC noted that no detail was provided in the PSCR on the methods used in the retrospective analysis such as the number of patients excluded and specific reasons for their exclusion, information on biomarker analysis (such as PD-L1 expression or tumour mutational burden) or other factors that may have determined treatment modality in the refractory setting. The pre-PBAC response noted the lack of national registry data and stated that VLCR data represented actual practices in this rare population. The pre-PBAC response argued that there was substantial use of ICI therapy in this patient population, driven predominately from intolerance to 2nd line chemotherapy regimens and the absence of targeted therapies.

- 5.3 The resubmission did not limit the chemotherapy comparator to taxanes. This was because only seven patients in the pooled chemotherapy cohort from Study 5002 and Study 5008 received taxanes (docetaxel n=5, paclitaxel n=2). To increase the sample size and therefore confidence in the comparison with mobocertinib, the entire chemotherapy cohort was used. In this cohort (N=23), eight patients received doublet PBC and 15 patients received single-agent chemotherapy including pemetrexed (n=7), docetaxel (n=5), paclitaxel (n=2) or gemcitabine (n=1). The ESC considered that the use of multiple forms of chemotherapy in this context was reasonable.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (2), health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website. The organisations comprised Rare Cancers Australia, Lung Foundation Australia, and the Medical Oncology Group of Australia (MOGA). The PBAC noted that this advice was supportive of the evidence provided in the submission.
- 6.3 The comments from individuals who have used this medicine for their own health condition described a range of benefits of treatment with mobocertinib including efficacy for their condition, the ability to return to work and largely manageable side effects. The comments from health care professionals indicated that mobocertinib was better tolerated than chemotherapy and that patients often responded better.
- 6.4 Rare Cancers Australia stated that patients with NSCLC *EGFR* ex20ins mutations are faced with an extremely poor prognosis, and commented better treatment options that provide significant improvements in survival were required. The organisation stated that the fear of progression, which this advanced stage population lives with, has severe mental-health and functioning impacts. The organisation described the rare and particularly aggressive nature of the disease, and highlighted that available evidence for mobocertinib suggests that treatment can significantly extend progression-free survival (PFS).
- 6.5 Lung Foundation Australia noted that mobocertinib is the first and only oral therapy specifically designed to target *EGFR* ex20ins mutations, providing a new and effective treatment for cancer patients with this specific mutation. The organisation noted that *EGFR* ex20ins mutation is uncommon and often underdiagnosed with a worse prognosis and survival outcomes compared to other *EGFR* mutations, which may be due to a lack of targeted therapies. The organisation stated that mobocertinib offers the opportunity to improve outcomes for [*EGFR* ex20ins mutation] lung cancer patients who have no other treatment options available.
- 6.6 The Medical Oncology Group of Australia (MOGA) also expressed its support for the mobocertinib submission. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for mobocertinib, which was limited to 2 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement),** based on a comparison with SOC.

Clinical studies

- 6.7 The resubmission presented the same studies (Studies 101, 5002 and 5008) as the original submission. Details of the studies included in the original submission and in the resubmission are provided in Table 3.

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

Table 3: Trials and associated reports presented in the submissions

Trial ID	Protocol title/ Publication title	Publication citation
Proposed medicine: mobocertinib		
Study 101 (NCT02716116)	Clinical Study Report. AP32788-15-101. A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral <i>EGFR/HER2</i> Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer.	15 January 2021
	Clinical Study Report Addendum 1. AP32788-15-101. A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral <i>EGFR/HER2</i> Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer.	03 May 2021
	Clinical Study Report Addendum 2. AP32788-15-101. A Phase 1/2 Study of the Safety, Pharmacokinetics, and Anti-Tumor Activity of the Oral <i>EGFR/HER2</i> Inhibitor TAK-788 (AP32788) in Non-Small Cell Lung Cancer.	19 April 2022
	Zhou C, Ramalingam S, et al. Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients with <i>EGFR</i> Exon 20 Insertion-Positive Metastatic Non-Small Cell Lung Cancer: A Phase 1/2 Open-label Non-randomized Clinical Trial.	<i>JAMA Oncology</i> 2021; 7(12): 1772-1781
Proposed comparator: SOC		
Study 5008 (Germany)	Final report of the study. Multicenter real-world analysis of non-small cell lung cancer patients with <i>EGFR</i> or <i>HER2</i> exon 20 insertion mutations. TAK-788-5008. Retrospective analysis. Final study report	14 January 2021.
	Study protocol. Multicenter Real World Analysis of Non-Small Cell Lung Cancer Patients with <i>EGFR</i> and <i>HER2</i> Exon 20 Insertion Mutations.	04 February 2019, Version 1.0.
Study 5002 (US Flatiron)	Clinical Study Report. TAK-788-5002. Retrospective Observational Study of Non-Small Cell Lung Cancer (NSCLC) Patients with <i>EGFR</i> Exon 20 Insertion Mutations: Real World Data Generation of Natural History.	19 January 2019, Version 1.0.
	Study Protocol. Retrospective Observational Study of Non-Small Cell Lung Cancer (NSCLC) Patients with <i>EGFR</i> Exon 20 Insertion Mutations: Real World Data Generation of Natural History.	14 July 2020, version 1.1
	Statistical Analysis Plan. TAK-788-5002. Retrospective Observational Study of Non-Small Cell Lung Cancer (NSCLC) Patients with <i>EGFR</i> Exon 20 Insertion Mutations: Real World Data Generation of Natural History.	15 July 2020, version 1.0.
Indirect comparison between mobocertinib and SOC or chemotherapy		
Study 101 vs. pooled Study 5002 and Study 5008	Technical report. IPTW of Mobocertinib vs. Standard of Care (SOC) in Advanced NSCLC Patients with <i>EGFR</i> EXON 20 Insertions. TAK-788-5010. Technical report of the IPTW of mobocertinib vs. SOC (Germany) using data from Study 101 at the 01 November 2020 cutoff	21 December 2021, Version 1.0.
	Comparison of Mobocertinib vs Usual care (GCR) using TAK-788-5008 data. Updated results of the IPTW of mobocertinib vs. SOC (Germany) using data from Study 101 at the 01 November 2021 cutoff	15 February 2022.
	Statistical Analysis Plan. IPTW of Mobocertinib vs. Standard of Care (SOC) in Advanced NSCLC Patients with <i>EGFR</i> EXON 20 Insertions. TAK-788-5010.	24 August 2021, Version 2.0.
	Study Report. Comparative Effectiveness of Mobocertinib and Standard of Care in Patients with NSCLC with <i>EGFR</i> Exon 20 Insertion Mutations: An Indirect Comparison.	09 November 2021.
	Comparison of Mobocertinib vs Usual care (FI) using TAK-788-5002 data. Updated results of the IPTW of mobocertinib vs. SOC (US Flatiron) using data from Study 101. Updated results of the IPTW of mobocertinib vs. SOC (US Flatiron) using data from Study 101 at the 01 November 2021 cutoff.	15 February 2022
	IPTW Mobo Nov2021 vs GCR+FI CHT. Min Tan, Thibaud Prawitz.	24 January 2023

Source: Table 2, pp11-12, Mobocertinib, public summary document (PSD), November 2022 PBAC meeting; mobocertinib resubmission. *EGFR*=epidermal growth factor receptor; Ex20ins=exon 20 insertion; FI=Flatiron; GCR=German Chart Review; IPTW=inverse probability treatment weighting; Mobo=mobocertinib; NSCLC=non-small cell lung cancer; SOC=standard of care comprising all treatments (*EGFR* TKI, ICI and chemotherapy); TAK-788=mobocertinib.

Blue shading indicates information previously seen by the PBAC.

- 6.8 The resubmission presented two unanchored indirect treatment comparisons (ITCs) using an inverse probability treatment weighting (IPTW) approach:
- Mobocertinib pooled prior platinum (PPP) cohort from Study 101 (N=114) versus the pooled SOC (comprising EGFR TKI, ICI and chemotherapy) cohort from Studies 5002 and 5008 (N=93); and
 - Mobocertinib PPP cohort from Study 101 (N=114) versus the pooled chemotherapy cohort from Study 5002 and Study 5008 (N=23).
- 6.9 The original submission presented ITCs of mobocertinib with SOC in Studies 5002 and Study 5008 separately. In November 2022, the ESC considered that comparing the PPP cohort of Study 101 with pooled results from the comparator studies 5002 and 5008 may be more reasonable than a comparison with either study alone as presented in the original submission (para 6.22, mobocertinib, PSD, November 2022 PBAC meeting). At that time, the PBAC considered that the resubmission should include a clinical analysis that measures an incremental benefit for mobocertinib compared with chemotherapy-based treatments (taxanes) (para 7.11, mobocertinib, PSD, November 2022 PBAC meeting). The resubmission presented an ITC of the mobocertinib PPP cohort from Study 101 versus the pooled chemotherapy cohort from Studies 5002 and 5008, as requested by the PBAC.
- 6.10 Key features of the study cohorts included in the ITCs are summarised in Table 4.

Table 4: Key features of the included evidence

Study	N	Design/Duration of follow up	Risk of bias	Patient population	Outcomes	Used in modelled evaluation
Mobocertinib						
Study 101 (DCO November 2021)	PPP cohort: 114 ^a	Single-arm, 25.8 months ^a	High	Patients with <i>EGFR</i> ex20ins variant advanced NSCLC, ≥ 1 prior treatment lines	PFS, OS, cORR,	–
SOC and chemotherapy						
Study 5008 ^b	SOC: 43 Chemotherapy: 11	Retrospective cohort study	High	Patients with <i>EGFR</i> ex20ins variant advanced NSCLC, ≥ 1 prior treatment lines	PFS, OS	–
Study 5002 ^c	SOC: 50 Chemotherapy: 12	Retrospective cohort study	High	Patients with <i>EGFR</i> ex20ins variant advanced NSCLC, ≥ 1 prior treatment lines	PFS, OS, ORR	–
Indirect comparison						
PPP cohort from Study 101 vs. pooled SOC cohort from Studies 5008 and 5002 ^d					PFS, OS, ORR	OS, PFS
PPP cohort from Study 101 vs. pooled chemotherapy cohort from Studies 5008 and 5002 ^d					PFS, OS, ORR	OS, PFS ^e

Source: Table 3, mobocertinib, PSD, November 2022 PBAC meeting; Section 2.2 of the resubmission.

DCO=data cut-off; *EGFR*=epidermal growth factor receptor; ex20ins=exon 20 insertion; NSCLC=non-small cell lung cancer; (c)ORR=(confirmed) objective response rate by Response Evaluation Criteria in Solid Tumours (RECIST v1.1); OS=overall survival; PFS=progression-free survival; PPP=pooled prior platinum; SOC=standard of care comprising all treatments (*EGFR* tyrosine kinase inhibitor, immune checkpoint inhibitor and chemotherapy)

^a Selected from three parts of Study 101 based on the following criteria: platinum pre-treated patients with *EGFR* ex20ins variant NSCLC who received the recommended mobocertinib dose of 160 mg once daily. Median treatment duration of 7.4 months.

^b German chart review; observation period 2013–2019.

^c US Flatiron registry data; observation period 2011–2020.

^d The risk of bias of the indirect comparisons was high, due to major transitivity issues across treatment cohorts indirectly compared.

^e OS and PFS data in the pooled chemotherapy cohort from Studies 5008 and 5002 were only used in a sensitivity analysis.

Blue shading indicates information previously seen by the PBAC.

6.11 Prior to IPTW, the comparator cohorts were “trimmed” by alignment with the inclusion/exclusion criteria of the Study 101 Extension cohort to improve the overlap in patient characteristics between the mobocertinib and comparator populations. Patients were selected from the comparator studies (*i.e.* Studies 5002 and 5008) for inclusion in the ITCs if they had initiated a line of therapy after they had a confirmed diagnosis of advanced NSCLC, and their tumours harboured an *EGFR* ex20ins mutation. Patients were excluded if they had an ECOG PS ≥ 2 and had received ≥ 3 systemic anticancer chemotherapy regimens for advanced NSCLC before the index therapy date (*i.e.* the date therapy was initiated after PBC). Patients from Study 5002 with a prior response to treatment with an *EGFR* TKI before the index therapy date were also excluded. It was unclear whether this criterion was applied to patients drawn from Study 5008.

6.12 The IPTW ITCs in the resubmission were conducted following guidelines from the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU)

for ITCs based on evidence from non-randomised studies^{††}. Population adjustment using IPTW should include known prognostic factors that are associated to an outcome, treatment-effect modifiers as well as any variables that affect the treatment-selection process. Prognostic variables selected for weighting were age, sex, smoking status, presence of brain metastases at baseline, and time since advanced diagnosis. Differences in study design between Study 101 and the comparator studies (prospective versus retrospective) had a significant impact on data collection (baseline data and assessment of outcomes). Retrospective data was less likely to be complete or accurate. This, in addition to the small number of patients included in the relevant comparator cohorts, limited the number of variables that could be adjusted in the IPTW and the reliability of the results. Additionally, there were differences in the timing of baseline data collection in the comparator studies such that collection of baseline characteristics was not comparable between the different study cohorts or representative of patient status at treatment initiation after PBC.

6.13 Patient demographics and disease characteristics of the mobocertinib PPP cohort from Study 101 (N=114) and the pooled chemotherapy cohort from the comparator studies (5008 and 5002) (N=23) are presented in Table 5.

Table 5: Baseline characteristics of the mobocertinib PPP cohort from Study 101 and the pooled chemotherapy cohort from Studies 5002 and 5008 before and after IPTW

Baseline parameter	Mobocertinib PPP cohort	Before IPTW			After IPTW		
		Chemotherapy cohort	P value	SMD	Chemotherapy cohort	P value	SMD
Sample size, N	114	23			115		
ESS	–	–	–	–	15.6	–	–
Age: mean (SD) ^a	59.6 (11.5)	63.8 (11.8)	0.112	0.363	58.1 (12.6)	0.6555	0.126
Sex = Female (%) ^a	75 (65.8)	14 (60.9)	0.832	0.102	64.8 (56.2)	0.4637	0.198
Smoking history: No n (%) ^a	81 (71.1)	12 (52.2)	0.128	0.398	84.28 (73.1)	0.8461	0.045
Brain metastases: No n (%) ^a	74 (64.9)	17 (73.9)	0.554	0.196	62.8 (54.4)	0.4372	0.215
Time since advanced diagnosis: mean (SD) ^a , months	15.7 (14.4)	12.8 (9.7)	0.355	0.238	13.4 (8.9)	0.3133	0.194

Source: Table 2-7, p13 of the resubmission.

ESS=effective sample size; N=number of patients; PPP=pooled prior platinum; IPTW=inverse probability of treatment weighting; SD=standard deviation; SMD=standardised mean difference.

^a Factors were included in the weighting.

Note: Outcome data was rounded to one decimal place.

6.14 The resubmission argued that, after weighting, baseline characteristics between the mobocertinib and chemotherapy cohorts were balanced, with a standardised mean difference (SMD) ≤ 0.25 . Although a SMD threshold of 0.25 is suggested in the NICE guidance, no justification was provided. There appears no universally agreed upon criterion as to what threshold of the SMD can be used to indicate an important imbalance. Other sources in the literature recommend a more stringent SMD

^{††} Faria R HA, Manca A, Wailoo AJ. NICE DSU Technical Support Document 17: The use of observational data to inform estimates of treatment effectiveness for Technology Appraisal: Methods for comparative individual patient data. <http://www.nicedsu.org.uk>. Published 2015. Accessed May 2023.

threshold of > 0.1 as an indication of important covariate imbalance^{††}. If this lower threshold is used, differences remained between the mobocertinib cohort and the pooled chemotherapy cohort after weighting for all the baseline characteristics except for smoking history, particularly for gender (female: 66% vs. 56%) and brain metastasis (yes: 35% vs. 46%).

- 6.15 The sample size of the pooled chemotherapy subgroup was artificially inflated from 23 to 115 via the IPTW. The effective sample size (ESS) of the chemotherapy cohort reduced to 15.6. As a result, correlation was induced within the chemotherapy cohort and there was a resulting lack of independence. It was unclear from the resubmission whether the IPTW weights were stabilised to account for extreme weighting and the inflated sample size.
- 6.16 The resubmission did not provide data on other important patient demographic and disease characteristics in the pooled chemotherapy cohort before and after weighting. The residual confounding due to unreported and, thus, unaccounted-for covariates, and the extent of this bias, cannot be assessed.
- 6.17 With regard to the pooled SOC cohort from Studies 5002 and 5008, weighting increased the sample size from 93 to 109 with an ESS of 65. There were notable differences in patient characteristics between the mobocertinib PPP cohort from Study 101 and the pooled SOC cohort from Studies 5002 and 5008 that could not be adjusted for in the IPTW, such as Asian race (60% vs. 7%-8%) and number of prior lines of therapy (≥ 2 lines: 59% vs. 4%-7%). In addition, there was a high risk of residual confounding across the Study 101 and pooled Studies 5002 and 5008 data sets due to other unobserved/unmeasured patient/disease characteristics, e.g. prior use of chemoradiotherapy and surgery (\pm adjuvant chemotherapy) in early-stage disease and ECOG PS.
- 6.18 Overall, the ESC considered the numerous limitations identified above (not exhaustive) cannot be adequately ameliorated using IPTW in the ITCs. The ESC agreed with the evaluation that there was a high degree of uncertainty regarding the indirect estimates of the incremental benefit of mobocertinib versus both chemotherapy and SOC.

Comparative effectiveness

- 6.19 The results of ITCs of mobocertinib *versus* the nominated comparator, *i.e.* chemotherapy, and *versus* SOC for OS and for PFS are presented in Table 6, along with the efficacy data previously reviewed by the PBAC at the November 2022 meeting. The OS and PFS Kaplan-Meier (KM) plots of OS and PFS for the ITC of mobocertinib *versus* chemotherapy are presented in Figure 1 and Figure 2.

^{††} Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med.* 2015 Dec 10;34(28):3661-79.

Table 6: Summary of the indirect comparison results in the resubmission and in the previous submission

	OS	PFS ^a
Study 101	Mobocertinib	
Median duration mobocertinib in Study 101 (N=114), months (95% CI)	20.2 (14.9, 25.3)	7.3 (5.6, 8.8)
Study 5008	SOC^b	
Unadjusted median duration in Study 5008 (N=43), months (95% CI)	11.3 (8.9, 14.5)	3.0 (2.0, 4.4)
IPTW adjusted median duration Study 5008 (95% CI)	9.8 (4.3, 13.7)	2.6 (1.5, 5.6)
Study 5002	SOC^b	
Unadjusted median duration Study 5002 (N=50), months (95% CI)	11.5 (7.9, 16.6)	3.3 (2.3, 5.9)
IPTW adjusted median duration Study 5002 (95% CI)	12.4 (7.1, 16.6)	3.25 (2.2, 7.3)
Pooled^c - Study 5008 and Study 5002	SOC^b	
Unadjusted median duration (N=93), months (95% CI)	11.4 (8.9, 14.1)	3.0 (2.5, 4.3)
IPTW adjusted median duration, months (95% CI)	11.0 (7.9, 13.6)	2.9 (2.2, 4.4)
Pooled - Study 5008 and Study 5002	Chemotherapy^d	
Unadjusted median duration (N=23), months (95% CI)	13.7 (9.4, 20.6)	5.0 (2.9, 8.1)
IPTW adjusted median duration, months (95% CI)	12.4 (8.9, 20.6)	4.4 (1.9, 8.1)
Indirect mobocertinib vs. SOC^b in Study 5008, (95% CI) [Log-rank p-value]		
Unadjusted HR	0.50 (0.32, 0.76) [0.0009]	0.34 (0.22, 0.51) [<0.0001]
IPTW adjusted HR	0.42 (0.26, 0.69) [0.0025]	0.28 (0.18, 0.43) [<0.0001]
Indirect mobocertinib vs. SOC^b in Study 5002, (95% CI) [Log-rank p-value]		
Unadjusted HR	0.58 (0.38, 0.88) [0.0120]	0.57 (0.37, 0.89) [0.0099]
IPTW adjusted HR	0.56 (0.37, 0.84)^a [0.0095]	0.58 (0.37, 0.91) [0.0207]
Indirect mobocertinib vs. pooled SOC^b cohort from Studies 5002 and 5008, (95% CI) [Cox p-value]		
Unadjusted HR	0.55 (0.39, 0.77) [0.0005]	0.46 (0.33, 0.64) [<0.0001]
IPTW adjusted HR	0.51 (0.35, 0.74) [0.0003]	0.49 (0.32, 0.75) [0.0012]
Indirect mobocertinib vs. pooled chemotherapy cohort from Studies 5002 and 5008^d, (95% CI) [Cox p-value]		
Unadjusted HR	0.69 (0.40, 1.17) [0.1671]	0.58 (0.36, 0.94) [0.0284]
IPTW adjusted HR	0.60 (0.34, 1.03) [0.0637]	0.50 (0.30, 0.82) [0.0059]

Source: Attachment 1 accompanying the resubmission; mobocertinib, public summary document, November 2022 PBAC meeting.

CI=confidence interval; HR=hazard ratio; IPTW=inverse probability treatment weighting; OS=overall survival; PFS=progression-free survival; SOC=standard of care.

^a As assessed by investigator in Study 101. Studies 5002 and 5008 were based on the German chart review and the US Flatiron databases, respectively, and thus PFS could not be categorised as either investigator or independent review committee assessed.

^b SOC included all treatments (epidermal growth factor receptor tyrosine kinase inhibitors, immune checkpoint inhibitors; and chemotherapy (platinum and non-platinum-based)).

^c Presented in the Pre-PBAC response for the previous submission.

^d 23 patients received chemotherapy: 8 received platinum-based chemotherapy and 15 patients received single-agent chemotherapy which included docetaxel (n=5), pemetrexed (n=7), paclitaxel (n=2) and gemcitabine (n=1).

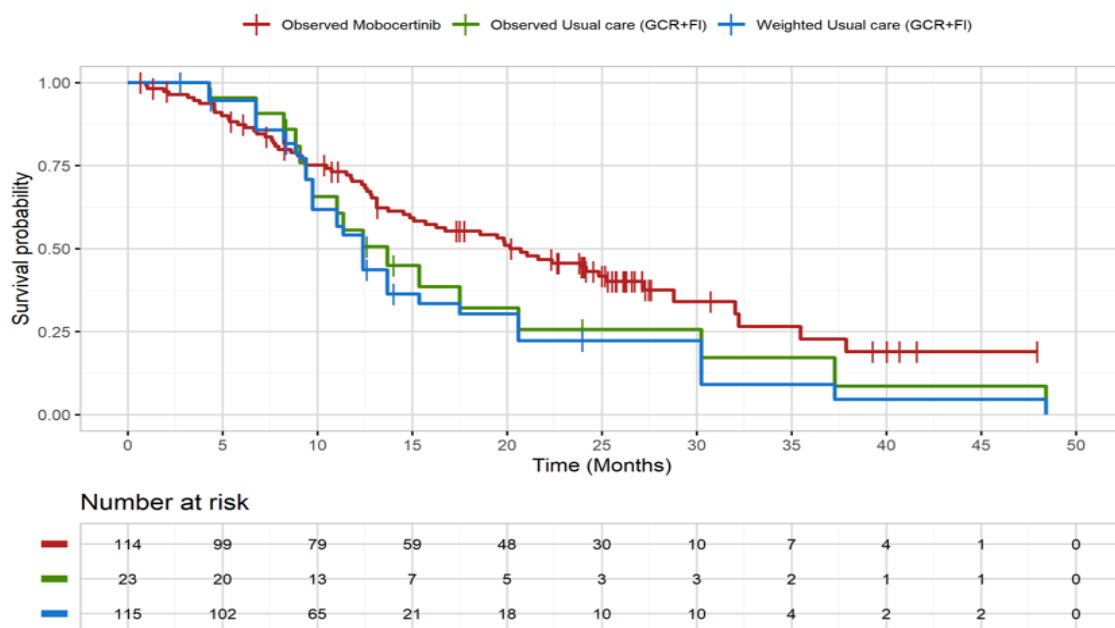
Notes: **Bolded results are statistically significant**

Mobocertinib data were based on the November 2021 data cutoff for Study 101. Median duration of follow-up 25.8 months.

Median durations rounded to one decimal place

Blue shading indicates information previously seen by the PBAC.

Figure 1: KM plot of OS for mobocertinib PPP cohort from Study 101 (observed) vs. pooled chemotherapy cohort from Studies 5002 and 5008 (unadjusted and IPTW adjusted)



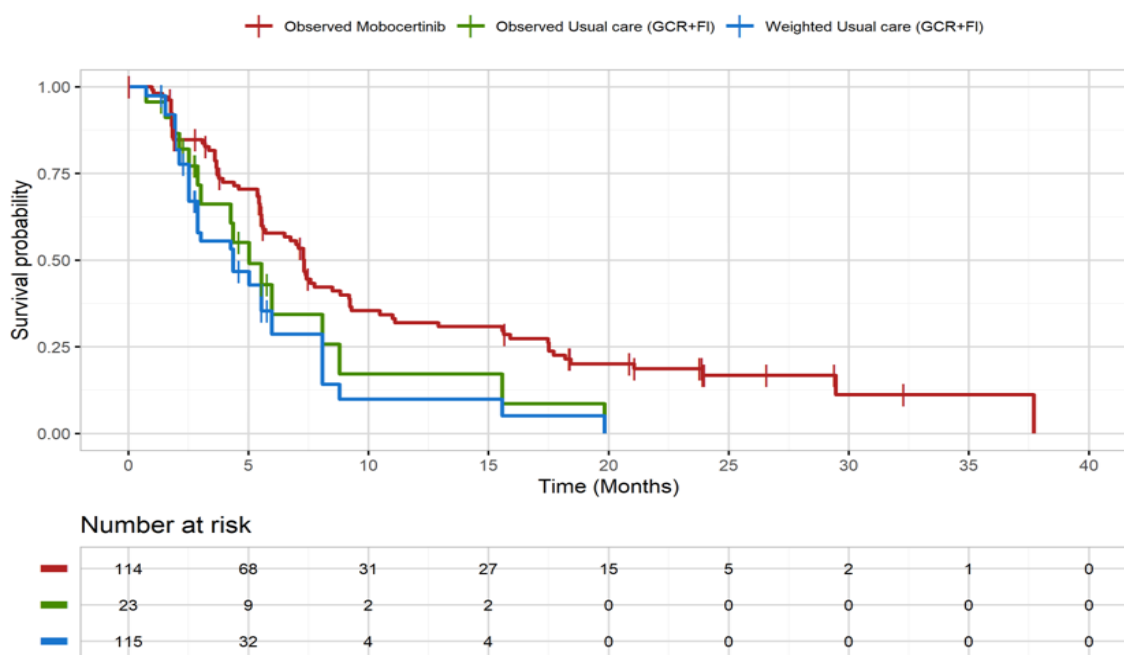
Source: Figure 2-3, p15 of the resubmission.

FI=US Flatiron registry data (used in Study 5002); GCR=German chart review data (used in Study 5008); IPTW=inverse proportional treatment weighting; KM=Kaplan-Meier; OS=overall survival.

Note:

Usual care in the figure legend refers to chemotherapy. Observed is OS as reported for the cohort (without adjustment by IPTW). Weighted is OS reported following adjustment by IPTW.

Figure 2: KM plot of PFS^a for mobocertinib PPP cohort (observed) from Study 101 vs. pooled chemotherapy cohort from Studies 5002 and 5008 (unadjusted and IPTW adjusted)



Source: Figure 2-4, p16 of the resubmission.

FI=US Flatiron registry data (used in Study 5002); GCR=German chart review data (used in Study 5008); IPTW=inverse proportional treatment weighting; KM=Kaplan-Meier; PFS=progression free survival

^a PFS as assessed by investigator in Study 101. Studies 5002 and 5008 were based on the German chart review and the US Flatiron databases, respectively, and thus PFS could not be categorised as either investigator or independent review committee assessed.

Note:

Usual care in the figure legend refers to chemotherapy. Observed is PFS as reported for the cohort (without adjustment by IPTW). Weighted is PFS reported following adjustment by IPTW.

6.20 The median OS was 20.2 (95% CI, 14.9, 25.3) months for mobocertinib compared with 13.7 (95% CI, 9.4, 20.6) months in the pooled chemotherapy cohort from Studies 5002 and 5008 before IPTW (events observed in 57.9% [66/114] versus 73.9% [17/23]). After IPTW, the median OS decreased slightly by 1.3 months (from 13.7 months to 12.4 months) in the pooled chemotherapy cohort. The reported OS hazard ratios (HRs) for mobocertinib versus chemotherapy was 0.69 (95% CI, 0.40, 1.17) before IPTW and 0.60 (95% CI, 0.34, 1.03) after adjustment; however, the differences did not reach statistical significance (Table 6). There is no indication in the resubmission that the proportional hazards assumption was tested. The OS KM curves for mobocertinib and for chemotherapy (both unadjusted and IPTW-adjusted) crossed at around Month 9 (Figure 1) indicating a violation of the proportional hazards' assumption. The ESC considered the indirect HR results, therefore, should be interpreted with a high degree of caution.

6.21 The median PFS was 7.3 (95% CI, 5.6, 8.8) months, as assessed by investigator, for mobocertinib, compared with 5.0 (95% CI, 2.9, 8.1) months in the pooled chemotherapy cohort (events observed in 69.3% [79/114] versus 69.6% [16/23]). After weighting, the median PFS slightly decreased in the chemotherapy subgroup from

5.0 months to 4.4 months. Both before and after IPTW, mobocertinib was associated with a statistically significant reduction in the risk of disease progression or death when compared to chemotherapy (unadjusted HR: 0.58 [95% CI, 0.36, 0.94]; IPTW adjusted HR: 0.50 [95% CI, 0.30, 0.82]) (Table 6).

- 6.22 The median OS for the pooled chemotherapy cohort, after IPTW adjustment, was slightly longer than that for the pooled SOC cohort (12.4 [95% CI: 8.9, 20.6] months versus 11.0 [95% CI: 7.9, 13.6] months), but the confidence intervals overlapped (Table 6). The point estimates of IPTW adjusted and unadjusted OS HRs were more favourable to mobocertinib if it was compared with SOC comprising all treatments (*EGFR* TKIs, ICIs and chemotherapy) than compared with chemotherapy alone (*e.g.* IPTW-adjusted HR: 0.51 [0.25, 0.74] *versus* 0.60 [0.34, 1.03]). A similar trend was observed for PFS. This could be attributable to the inclusion of ICIs and standard *EGFR* TKIs in the comparator cohort which are less effective as second-line treatment of *EGFR* ex20ins positive NSCLC. ICIs and standard *EGFR* TKIs accounted for around 70% of therapies in the pooled SOC cohort drawn from German and US patient populations, but are not commonly used in Australian clinical practice in the second-line *EGFR* ex20ins NSCLC setting (para 6.53, mobocertinib, PSD, November 2022 PBAC meeting).
- 6.23 Any interpretation of the indirect results of mobocertinib versus chemotherapy or versus SOC should consider the limitations associated with the IPTW unanchored indirect comparisons, which are discussed in the “Clinical studies” section.

Comparative harms

- 6.24 No comparative safety data are presented in the original submission or in the resubmission for mobocertinib *versus* chemotherapy or *versus* SOC.
- 6.25 A summary of overall safety outcomes in the PPP cohort of Study 101 (as presented in the original submission) is presented in Table 7.

Table 7: Summary of overall AEs (any grade or Grade ≥ 3) for the mobocertinib PPP cohort from Study 101

AE, n (%)	Any grade	Grade ≥ 3
Any TEAE ^a	114 (100)	86 (75)
Drug-related	113 (99)	59 (52)
Leading to treatment discontinuation	21 (18)	NA ^c
Leading to dose reduction	31 (27)	NA ^c
Any TESAE	60 (53)	55 (48)
Drug-related	22 (19)	20 (18)
Leading to treatment discontinuation	11 (10)	NA ^c
Leading to dose reduction	3 (3)	NA ^c
Deaths ^b	15 (13)	

Source: Table 10, mobocertinib, PSD, November 2022 PBAC meeting.

AE=adverse event; NA=not available/applicable; PPP=pooled prior platinum; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event.

^a TEAEs are all AEs with an onset date on or after the first dose date and within 30 days of last dose of study drug. AEs were graded according to the National Clinical Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Patients were counted only once in their most severe category. Medical Dictionary for Regulatory Activities (MedDRA) Dictionary (Version 24.0) was used for coding AEs.

^b Death within 30 days of last dose.

^c Not evaluated by AE grade

Data cutoff: November 2021.

Blue shading indicates information previously seen by the PBAC.

- 6.26 The most frequently reported treatment-emergent adverse events of any grade (>30% of patients) included diarrhoea (93%), rash (47%), decreased appetite (45%), vomiting (43%), nausea (40%), paronychia (39%), blood creatinine increased (35%), anaemia (34%), and dry skin (33%) (para 6.36, mobocertinib, PDS, November 2022 PBAC meeting). Overall, the safety of mobocertinib observed in Study 101 appeared to be similar to that of other *EGFR* inhibitors which is typically characterised by gastrointestinal-related and cutaneous-related AEs.
- 6.27 Interpretation of the safety data from Study 101 should be made in the context of the open-label design and stringent exclusion criteria of Study 101 (such as patients with a history of interstitial lung disease (ILD), drug-related or radiation-related pneumonitis that required steroid treatment, or active cardiovascular disease/prolonged QTc interval). The safety data from Study 101 are likely to overestimate the safety of mobocertinib in clinical practice.
- 6.28 The mobocertinib Product Information included special warnings and precautions for use for QTc prolongation and Torsades de Pointes, ILD/pneumonitis, cardiac failure, and diarrhoea.

Benefits/harms

- 6.29 A benefits/harms quantification table is not presented. The results of the unanchored IPTW-based indirect comparisons were associated with a high risk of bias and there were important observed differences across mobocertinib and comparator cohorts that could not be adjusted for, and the impact of unknown confounders remained unclear. This leads to a high level of uncertainty regarding the magnitude of any incremental benefit associated with mobocertinib over chemotherapy or SOC

comprising all treatments (standard *EGFR* TKIs, ICIs and chemotherapy). There were no comparisons made for safety.

Clinical claim

- 6.30 The resubmission described mobocertinib as superior in terms of effectiveness compared to SOC in patients with locally advanced or metastatic NSCLC and *EGFR* ex20ins mutations who have progressed on or following prior treatment with PBC. In the clinical evaluation section of the resubmission, SOC referred to all treatments (standard *EGFR* TKIs, ICIs and chemotherapy). The ESC agreed with the evaluation that this claim was not adequately supported by the available evidence. Results of the IPTW-based indirect comparisons to SOC were associated with a high risk of bias and the magnitude of the treatment benefit associated with mobocertinib was uncertain and likely overestimated in the Australian setting due to the inclusion of ICIs and standard *EGFR* TKIs which are not effective in the proposed *EGFR* ex20ins NSCLC population. However, the IPTW-based indirect comparisons of mobocertinib versus chemotherapy alone were also associated with a high risk of bias and uncertainty around the comparative treatment benefit.
- 6.31 The resubmission presented two IPTW-based unanchored ITCs: 1) comparing the mobocertinib PPP cohort from Study 101 *versus* the pooled chemotherapy cohort from Studies 5002 and 5008; and 2) comparing the mobocertinib PPP cohort from Study 101 *versus* the pooled SOC cohort from Studies 5002 and 5008.
- 6.32 The key issues associated with these ITCs were:
- The study design differed between Study 101 (prospective) and Studies 5008 and 5002 (retrospective). There were differences in collection of data (prospective versus retrospective) and the methods of treatment response assessment. Retrospective data were more likely to be incomplete and less accurate. This, in addition to the small sample size of the pooled cohorts from Studies 5008 and 5002, especially the pooled chemotherapy cohort (N=23), limited the number variables that could be adjusted for in the IPTW. The ESS of the chemotherapy cohort reduced to 15.6 after IPTW.
 - Differences remained after IPTW adjustment between the mobocertinib and chemotherapy cohorts in terms of some variables selected for weighting, such as gender and brain metastasis.
 - There were large imbalances for some characteristics between Study 101 and the retrospective Studies 5002 and 5008 which could not be adjusted for (e.g. Asian race and number of prior lines of therapy) using IPTW in the ITCs.
 - There was a high risk of residual confounding due to other unobserved/unmeasured patient and study characteristics across the mobocertinib and retrospective comparator cohort data sets.

- 6.33 The resubmission claimed that mobocertinib has a different safety profile compared to chemotherapy or immunotherapy and that its safety profile is acceptable and similar to that of other TKIs. No formal indirect comparisons of safety were presented in the resubmission or in the original submission. When the previous submission was reviewed, the ESC considered that it is unclear but likely that mobocertinib has an acceptable safety profile that is similar to other TKIs. The PBAC previously noted the submission did not present a safety comparison of mobocertinib against SOC, and considered that mobocertinib may have a “different” safety profile that is not non-inferior to SOC (para 6.48 and 7.7, mobocertinib, PSD, November 2022 PBAC meeting). The ESC noted that no new safety evidence was presented and reiterated its November 2022 advice that it is unclear but likely that mobocertinib has an acceptable safety profile that is similar to other TKIs.
- 6.34 The PBAC agreed with the evaluation and the ESC, that the data presented was associated with a high risk of bias and uncertainty around the comparative treatment benefits for mobocertinib versus SOC or versus chemotherapy. However, acknowledging the data limitations, the PBAC considered the claim of superior effectiveness compared to SOC was uncertain but likely reasonable in this a rare subset of *EGFR* mutations.
- 6.35 The PBAC considered that the claim that mobocertinib has a different safety profile compared to chemotherapy or immunotherapy and that its safety profile is acceptable and similar to that of other TKIs was reasonable.

Economic analysis

- 6.36 The resubmission presented a stepped economic evaluation comparing mobocertinib versus SOC for the treatment of patients with locally advanced or metastatic (Stage IIIB-IV) NSCLC with *EGFR* ex20ins mutations who have previously received PBC based on an indirect comparison of retrospective cohort studies. A cost-effectiveness analysis and a cost-utility analysis were presented measuring outcomes in terms of life years (LYs) gained and quality-adjusted life years (QALYs) gained, respectively. The key components of the economic evaluation and justifications for the approach provided by the submission are presented in Table 8.
- 6.37 The key changes considered in the resubmission include;
- Use of pooled KM data from studies 5002 and 5008
 - Application of only chemotherapy costs for comparator and subsequent treatments
 - Revised proposed price of mobocertinib (reduced by 10%).

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

Component	Description
Type of analysis	Cost-utility analysis
Outcomes	Life years gained, quality-adjusted life years gained
Time horizon	5 years
Methods used to generate results	Three health state partitioned survival model
Health states	Progression-free; Progressed disease; Dead
Cycle length	28 days - reflects the duration of treatment per pack of mobocertinib dispensed.
Health state allocation	<p>Mobocertinib arm: PFS (IRC) and OS from Study 101 (PPP cohort).</p> <p>Comparator arm: Weighted (pooled) PFS and OS from Study 5008 and Study 5002 where SOC included all treatments (TKIs, immunotherapies or chemotherapies) in the base case.</p> <p>The resubmission stated that using a chemotherapy only sub-population resulted in a small sample size with wide confidence intervals around the median OS, PFS and TTD values, therefore given the uncertainty, data from this subpopulation was restricted to use in sensitivity analyses.</p>
Extrapolation method	In both the arms KM data are used up until study follow-up (36 months) and extrapolated out to the modelled time horizon, then there is a forced linear convergence in the mobocertinib arm from 36 months to 0% survival at the 5-year time horizon.
Utilities	<p>Utilities derived from Part 3^a of Study 101 (EXCLAIM) were applied across both arms of the model.</p> <p>HRQoL data were not collected in the retrospective cohort studies (5008 or 5002).</p> <p>Utility decrements are applied for Grade ≥ 3 AEs in each treatment arm.</p>

Source: constructed during the evaluation based on first submission and the resubmission

AE = adverse event; EGFR = epidermal growth factor receptor; ex20ins = exon 20 insertion; HRQoL = health-related quality of life; IRC = independent review committee; OS = overall survival; PFS = progression free survival; PPP = pooled prior-platinum; SOC = standard of care; USA = United States of America

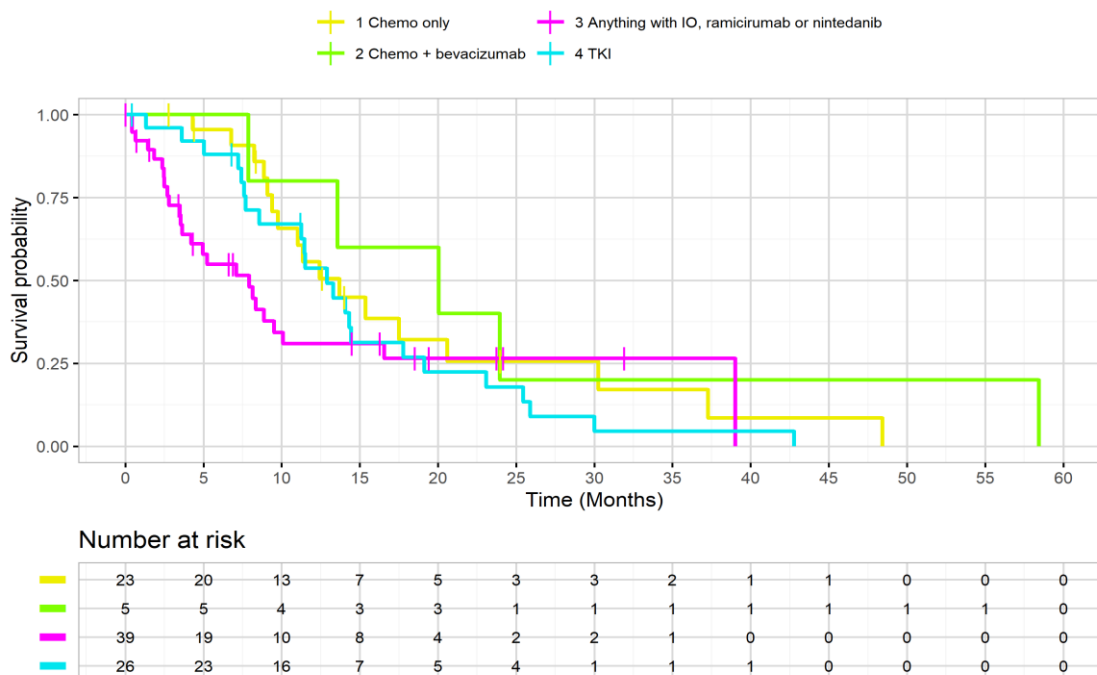
^a Study 101 included three parts: Part 1 (dose escalation cohort, N=73), Part 2 (expansion cohort, N=136) and Part 3 (extension cohort, N=96). The PPP cohort of Study 101 (N=114) were mainly from Part 3 (n=86), followed by Part 2 (n=22) and Part 1 (n=6).

Blue shading indicates components remaining unchanged since the previous submission.

- 6.38 The resubmission used a partitioned survival approach where the total time spent in each health state of the model was calculated from the area under the PFS and/or OS curves. The approach taken in the resubmission remained the same as in the previous submission. In the base case analysis, the submission used the observed (weighted) KM data up until 36 months (39 cycles) in both the arms for OS and PFS. Independent parametric survival models were fitted to available KM data for mobocertinib and comparator arms for PFS, OS and TTD curves. Observed data is reasonably mature and extrapolations had little impact on the model. The model applied a convergence function from 36 months, which partly replaces the parametric function for PFS and entirely replaces the parametric function for OS and for TTD.
- 6.39 In November 2022, the ESC considered that a comparison of mobocertinib with pooled results from studies 5008 and 5002 may be more reasonable than a comparison with either study alone (paragraph 6.22, mobocertinib PSD, November 2022 PBAC meeting). Therefore, the resubmission applied the pooled results from studies 5002 and 5008 (with equal weighting) to estimate PFS, OS and TTD in the comparator arm.

- 6.40 In November 2022, the ESC also acknowledged that agents currently used in Australian clinical practice in the second-line treatment setting for advanced NSCLC include docetaxel, gemcitabine, pemetrexed, carboplatin and paclitaxel (paragraph 6.22, mobocertinib PSD, November 2022 PBAC meeting). The resubmission assumed chemotherapy comprising above treatments as comparator. Therefore, costs and outcomes must be specific to chemotherapy.
- 6.41 The modelled survival outcomes based on pooled data (from studies 5002 and 5008) in the resubmission were again informed by treatments (TKIs, ICIs or chemotherapies) that likely do not reflect current Australian clinical practice. The revised model is not restricted to the use of only the chemotherapy patient survival data from studies 5002 and 5008. The resubmission and PSCR assumed any differences in outcomes between chemotherapy and other regimens are more likely to be artefacts of small patient numbers, chance and/or selection biases, however this is unknown.
- 6.42 Pooled KM estimates of observed OS segregated by treatment class (Figure 3 and Table 9) suggest patients treated with immunotherapies and TKIs had poor OS compared to patients treated with chemotherapy only. As the number of patients in these subgroups (n = 65) are higher than the patients treated with chemotherapy only (n = 23), survival estimates from pooled SOC (from studies 5002 and 5008 with all treatments) applied in the model are dominated by immunotherapies and TKIs. This brings down the OS in the comparator arm and overestimating the incremental benefit. The evaluation considered this favoured mobocertinib. Consequently, applicability of the pooled survival results from these studies based on all treatments is uncertain. The PSCR stated the base case analysis in the resubmission captured the intent of the PBAC's desire for a comparison against chemotherapy by assigning chemotherapy as the proxy for the cost of SOC. The PSCR argued that irrespective of the choice of survival curves, the choice of comparator costs was a greater driver of the ICER. The PSCR stated that VLCR data indicated ICI treatment is used in this patient population and highlighted that increasing the use of immunotherapies in the cost of the comparator would reduce the ICER. The ESC noted the November 2022 PBAC advice was not to assign chemotherapy as the proxy for the cost of SOC but to consider chemotherapy as SOC. In addition, the ESC noted that there is limited evidence regarding the benefit of ICI monotherapy in the proposed target population and current treatment guidelines do not recommend ICI treatments in *EGFR* positive tumours. The ESC agreed with the evaluation that use in the model of survival estimates from pooled SOC favoured mobocertinib. Therefore, the ESC considered both the survival estimates and costs in the comparator arm should be based on chemotherapy alone. The pre-PBAC response argued that limiting the analysis to the 23/93 patients receiving chemotherapy, means that inferences are being made about the relative merits of individual treatments. The pre-PBAC response stated that relying on the underpowered subgroup analyses leads to the conclusion that chemotherapy is superior to all other non-chemotherapy agents in the SOC arm in this setting which the sponsor argued was untrue.

Figure 3: Pooled KM estimates of observed OS segregated by treatment class



Source: Attachment 1 provided with the resubmission

Table 9: Median overall survival by treatment class

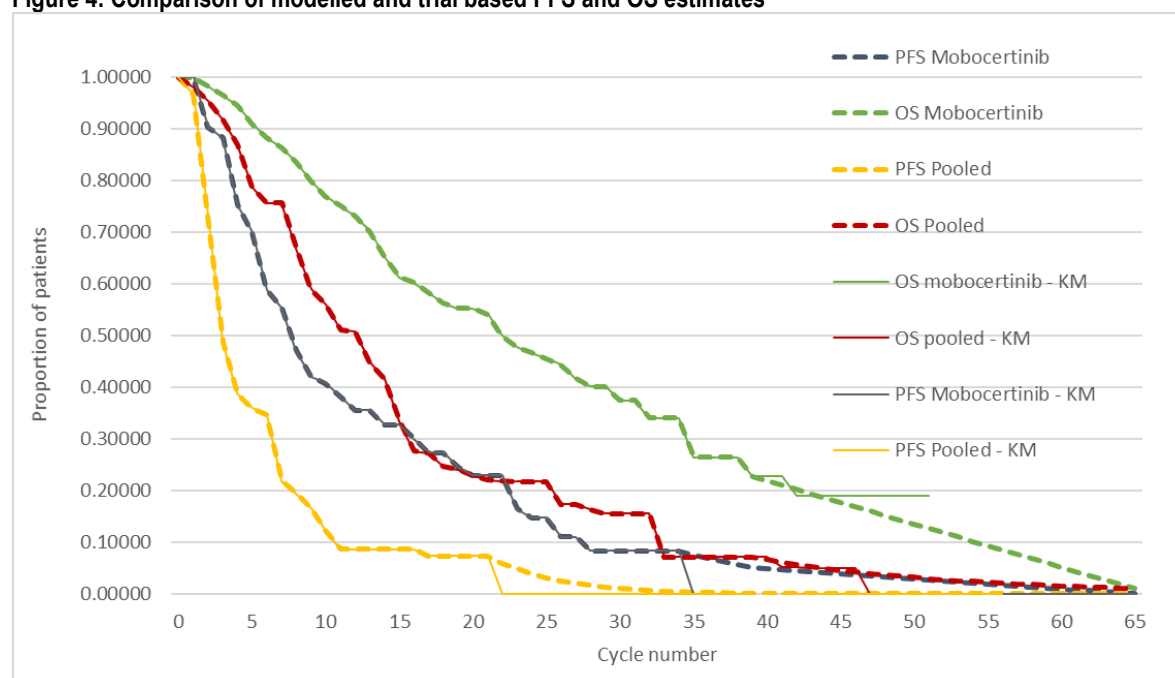
Comparison	Records	N. Max	Number of events	Median time to event	Lower 95%CI	Upper 95%CI
Chemo only	23.0000	23.0000	17.0000	13.7002	9.3963	20.5996
Chemo + bevacizumab	5.0000	5.0000	5.0000	20.0411	7.8850	NA
Anything with IO, ramucirumab or nintedanib	39.0000	39.0000	25.0000	7.9179	3.5483	10.0862
TKI	26.0000	26.0000	23.0000	12.9117	7.6879	17.7741

Source: Attachment 1 provided with the resubmission

Chemo = chemotherapy; IO = immunotherapy; TKI = tyrosine kinase inhibitors.

6.43 A comparison of the trial-based (post-IPTW for the comparator arm) and the modelled survival curves (Figure 4) indicated that most of the observed trial data have been used to inform the modelled curves, and extrapolation and point of truncation have only a minor impact on the survival outcomes.

Figure 4: Comparison of modelled and trial based PFS and OS estimates



Source: Figure constructed during the evaluation, based on 'Section 3 CE Model Workbook – Takeda Australia – Mobocertinib – Resubmission – March 2023'

KM = Kaplan-Meier; Mobo = mobocertinib; OS = overall survival; PFS = progression free survival

6.44 The model applied a per cycle adverse event (AE) treatment cost calculated based on the rate of AEs per cycle. To determine the rate of AEs per cycle, the number of patients experiencing each AE was divided by the number of patient weeks of exposure (calculated from the median duration of treatment from the trial) and multiplied by 4 weeks (model cycle length). It is more appropriate to use mean duration of treatment instead of median for cost estimation purposes, and these will differ where the distribution is skewed; this was noted in the evaluation of the original submission, however not recalculated at that time. Applying the mean treatment durations for both arms based on TTD data from the economic model workbook increased the ICER by 9% to \$75,000 to < \$95,000/QALY (base case ICER - \$55,000 to < \$75,000/QALY). The ESC considered the use of mean treatment durations for AE cost estimation purposes was appropriate.

6.45 The model applied health state resource costs which were derived based on health care resource utilisation reported in Lee et al^{§§}. The resubmission adjusted rate of hospitalisation and outpatient visits reported in the Lee study to avoid double counting in PFS. This resulted in a negative outpatient visit cost (i.e. rebate) which is not reasonable. In addition, it is not clear why the submission adjusted the rate of hospitalisation and outpatient visits in the progressed disease state using the rate of AE and anticancer administrations specific to PFS, when these costs had not been

^{§§} Lee DH, Isobe H, Wirtz H, Aleixo SB, Parente P, de Marinis F, et al. Health care resource use among patients with advanced non-small cell lung cancer: the PIVOTAL retrospective observational study. *BMC Health Serv Res.* 2018;18(1):147.

added to the subsequent treatment costs. The evaluation tested the impact of not making these adjustments to the estimated health state costs in a sensitivity analysis; this increases the ICER by 11% to \$75,000 to < \$95,000/QALY (base case ICER – \$55,000 to < \$75,000/QALY). The PSCR argued the recalculations for the health state costs are not necessary and inappropriately result in the double counting not being corrected for. The ESC considered it was appropriate to adjust rate of hospitalisation and outpatient visits to avoid double counting in the progression-free state. However, the ESC agreed with the evaluation that adjustment to the extent of applying a ‘negative’ outpatient visit cost (i.e. rebate) is not reasonable. The outpatient visit rate (1.163/cycle in progression-free state and 2.736/cycle in progressive disease state) in the Lee et al (2018) study suggested that those estimates were based on a more generalised patient cohort with less intensive treatment than the modelled patient cohort, but this does not mean that the modelled allocation of outpatient visits – based on administration rates specific to the treatments being evaluated – has been overestimated. The ESC considered the outpatient visit estimate in Lee et al (2018) can be disregarded and neither an additional health state cost nor ‘rebate’ based on outpatient use should be included in the health state resource costs.

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

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: \$■/QALY gained
Choice of comparator survival estimates	Using KM data from a basket of treatments (EGFR TKIs and immunotherapies) as the basis for TTD, PFS and OS estimates rather than just chemotherapy patient data.	Moderate, base case favours mobocertinib Limiting the survival estimates to only chemotherapy regimens used in the model base case increased ICER to \$■ ² /QALY gained.

Source: Compiled during the evaluation based on Section 3 of the resubmission

EGFR = epidermal growth factor receptor; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$95,000 to < \$115,000

6.47 The results of the stepped economic evaluation presented in the resubmission are summarised in Table 11. The steps that had the most impact on the model estimates were limiting the comparator costs to chemotherapy only (Step 3) and reduction in the price of mobocertinib (Step 6).

Table 11: Results of the stepped economic evaluation – model base case

Step and component	Mobocertinib	Comparator	Increment
Step 1: Base case of original submission (November 2022)			
Costs	\$█	\$74,086.64	\$█
QALYs	1.528	0.797	0.7313
Incremental cost/extra LYG gained			\$ ¹
Step 2: Use of pooled KM data from studies 5002 and 5008			
Costs	\$█	\$82,880.50	\$█
QALYs	1.535	0.924	0.6108
Incremental cost/extra LYG gained			\$ ²
Step 3: Chemo only comparator costs			
Costs	\$█	\$53,728.89	\$█
QALYs	1.535	0.924	0.6108
Incremental cost/extra LYG gained			\$ ³
Step 4: Chemo only subsequent treatment costs			
Costs	\$█	\$44,473.25	\$█
QALYs	1.535	0.924	0.6108
Incremental cost/extra LYG gained			\$ ⁴
Step 5: No half cycle correction applied to treatment costs			
Costs	\$█	\$44,655.36	\$█
QALYs	1.535	0.924	0.6108
Incremental cost/extra QALY gained (base case)			\$ ⁵
Step 6: Update to price of mobocertinib (reduced by █%)			
Costs	\$█	\$44,655.36	\$█
QALYs	1.535	0.924	0.6108
Incremental cost/extra QALY gained (base case)			\$ ⁵

Source: Compiled during the evaluation based on the on 'Section 3 CE Model Workbook – Takeda Australia – Mobocertinib – Resubmission – March 2023'

LYG = life year gained; QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$95,000 to < \$115,000

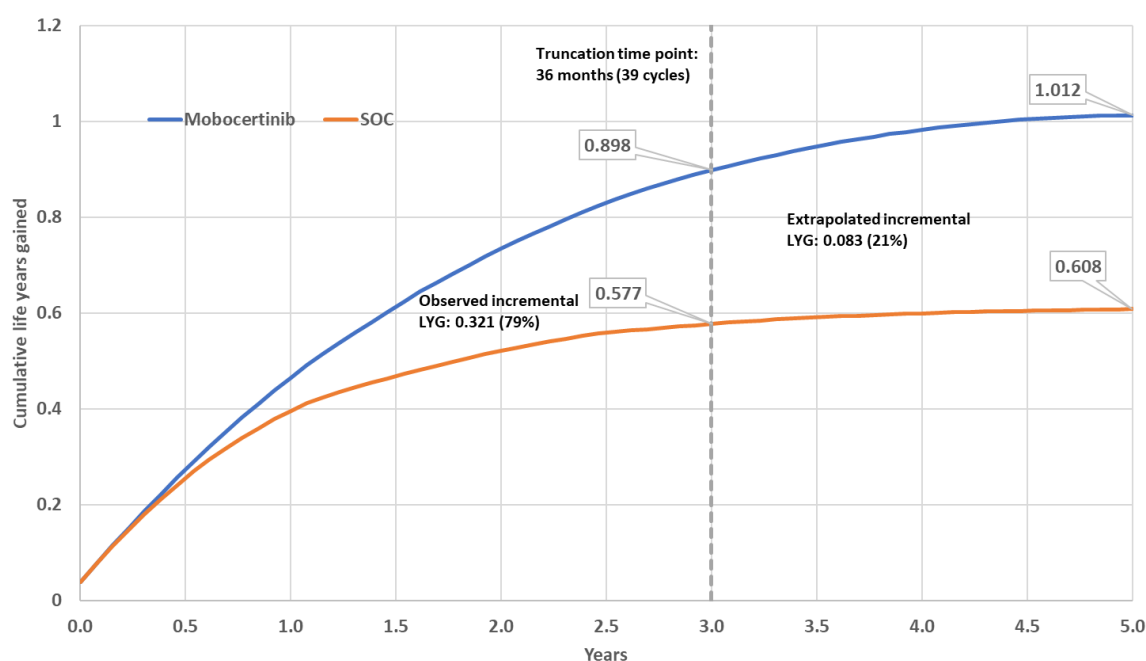
³ \$135,000 to < \$155,000

⁴ \$115,000 to < \$135,000

⁵ \$55,000 to < \$75,000

6.48 Cumulative LYs gained over the time horizon is depicted in Figure 5. Only 21% of the incremental LYs were accrued in the extrapolation period.

Figure 5: Cumulative life years gained over the time horizon of the model (discounted)



Source: Constructed during the evaluation based on the on 'Section 3 CE Model Workbook – Takeda Australia – Mobocertinib – Resubmission – March 2023'

LYG = life years gained.

6.49 The results of key sensitivity analyses are summarised in Table 12.

6.50 Additional sensitivity analyses conducted during the evaluation significantly increased the ICER; when only chemotherapy KM data is considered as the basis for survival estimates, the ICER increased to \$95,000 to < \$115,000 per QALY. Adjustment to the calculation of the AE costs based on mean treatment duration and adjustment to outpatient visit rates within the health state costs (without changing the comparator), increased the ICER to \$75,000 to < \$95,000 per QALY. Applying all of these changes, simultaneously, inflated the ICER to \$95,000 to < \$115,000 per QALY. The ESC considered the appropriate base case analysis should include the chemotherapy only subpopulation, adverse event costs and health state resource costs. The ESC noted that this increased the base case ICER by 41% from \$55,000 to < \$75,000 to \$95,000 to < \$115,000 per QALY gained. The pre-PBAC response argued that the base case estimate in the resubmission which uses the low cost of chemotherapy together with the most complete evidence for comparative OS provides the most reliable and sufficiently conservative estimate of the cost-effectiveness of mobocertinib.

Table 12: Sensitivity analyses

Analyses	Incremental cost	Incremental QALY	ICER	% change to ICER
Base case	\$█	0.6108	█ ¹	-
KM data used - Chemotherapy alone				
1. Weighted	\$█	0.2395	█ ³	38%
Discount rate (base case 5% costs and outcomes)				
2. 0%	\$█	0.675	█ ¹	-0.65%
3. 3.5%	\$█	0.629	█ ¹	-0.20%
Adverse event costs (base case: included with median Tx durations)				
4. Applying mean Tx durations	\$█	0.611	█ ²	9%
Health state resource costs (base case: Rate of hospitalisation and outpatient visits adjusted in both health states)				
5. Without adjusting rate of hospitalisation and outpatient visits in PFS and progressed disease state	\$█ ^a	0.611	█ ²	11%
Multivariate Analysis – Potential base case re-specification				
Inputs adjustments as per analyses 4,5	\$█ ^a	0.611 ^a	█ ²	18%
Use of chemotherapy patient KM data only in the comparator arm and adjustments 4,5	\$█ ^a	0.240 ^a	█ ³	41%

Source: Analyses conducted during the evaluation based on the on 'Section 3 CE Model Workbook – Takeda Australia – Mobocertinib – Resubmission – March 2023'

KM = Kaplan-Meier; PFS = progression free state; QALY = quality adjusted life year, ICER = incremental cost=effectiveness ratio

^a Corrected during the preparation of the ESC Advice.

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

³ \$95,000 to < \$115,000

Drug cost/patient/course

6.51 A comparison of the drug costs of mobocertinib and chemotherapy estimated based on the trial data, the economic evaluation and the financial analysis is presented in Table 13.

Table 13: Drug cost per patient for mobocertinib and standard of care

	Mobocertinib			Chemotherapy alone		
	Trial dose and duration	Model	Financial estimates	Trial dose and duration	Model	Financial estimates
Mean dose	160 mg/day	160 mg/day	160 mg/day	NR	NR	NR
Dose intensity	91.81% ^a	93% ^c	93% ^c	93% ^c	93% ^c	93% ^c
Mean duration (28-day cycles)	7.995 (median) ^b	13.34 ^d	12.79 ^e	NR	5.43 ^d	4.93 ^e (4.84) ^g
Cost/patient/cycle	\$	\$	\$	NA	\$364 (\$327.93) ^f	\$178 ^h (\$350.62) ^h
Cost/patient/ /course	\$	\$	\$	NA	\$1,976 (\$1,780) ^f	\$786 ⁱ (\$1,697) ^j

Source: Compiled based on 'Section 3 CE Model Workbook – Takeda Australia – Mobocertinib – Resubmission – March 2023' and 'Section 4 UCM Workbook – Takeda – Australia – Mobocertinib – Resubmission – March 2023'.xlsx'

NR=not reported in the submission, NA = not available

^a Mean relative dose intensity in the pooled prior platinum cohort in Study 101 (N=114), sourced from Section 4.3.1 of '2.3 AP32788-15-101 CSR Addendum 2'

^b The submission provided median duration (7.8 months) only. Sourced from Section 4.3.1 of '2.3 AP32788-15-101 CSR Addendum 2'

^c The economic evaluation and the financial analysis used the mean relative dose intensity for mobocertinib in Part 3 of Study 101 (N=96). The submission assumed the same relative dose intensity for the comparator treatments.

^d Sourced from 'Section 3 CE Model Workbook – Takeda Australia – Mobocertinib'

^e Sourced from 'Section 4 UCM Workbook – Takeda – Australia – Mobocertinib.xlsx'

^f After correcting for dosage and duration of Paclitaxel

^g Based on chemotherapy only TTD from studies 5002 and 5008

^h Calculated by dividing cost/patient/course with mean duration.

ⁱ Calculated by changing number of patients on treatment in one of the years to '1' and other years to '0'.

^j Revised result after correcting the resubmission's errors in referencing adjusting for distribution of individual drugs and duration of treatments.

Estimated PBS usage & financial implications

6.52 This submission was not considered by DUSC.

6.53 The submission used an epidemiological approach to estimate the number of patients eligible for treatment with mobocertinib. A summary of the data sources and parameter values used to estimate the utilisation and financial implications associated with the listing of mobocertinib is provided in the Table 14. In its November 2022 meeting, the PBAC considered that a resubmission for mobocertinib should present revised financial estimates consistent with DUSC advice for:

- i. the proportion of patients with Stage IIIB/IV NSCLC
- ii. the prevalence of *EGFR* ex20ins
- iii. the number of prevalent patients (para 6.81, Mobocertinib PSD, November 2022 PBAC meeting).

In addition to this, in November 2022 the PBAC noted the estimated cost offsets to PBS/RPBS are likely to have been overestimated (paragraph 6.82, Mobocertinib PSD, November 2022 PBAC meeting) and the revised financial estimates should exclude the use of *EGFR* TKIs and ICI monotherapy.

6.54 The resubmission addressed these concerns and reviewed the inputs which the evaluation considered were well supported by reasonable sources of information.

Table 14: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Incidence of Lung cancer	14,724 in Year 1 of listing (2024), increasing to 16,385 in Year 6 (2028)	AIHW - Cancer report 2021 (for incidence data in 2021: 13,810) and Osimertinib PSD, July 2020 PBAC meeting (for an annual growth rate of 2.16%)	Reasonable data sources
Proportion of lung cancer reported as NSCLC	86.6%	Mitchell 2013	Reasonable The PBAC previously accepted a proportion of 86.6% in the entrectinib submission (Entrectinib PSD, March 2020 PBAC Meeting).
Proportion with Stage IIIB-IV disease	65.5%	Mitchell 2013	Reasonable data source
Proportion of patients diagnosed at stage IIIA disease	11.8%	Mitchell 2013	Reasonable data source
Proportion of Stage IIIA disease that progresses to Stage IIIB or Stage IV over one year	60%	Table 17, Pembrolizumab PSD, November 2018 PBAC meeting	Reasonable data source
Patients with successful biopsy and biomarker testing	90%	MSAC application 1173 PSD, August 2012 (Moore 2018)	Reasonable
Patients with <i>EGFR</i> mutations	17.90%	DUSC review on erlotinib and gefitinib (2017)	Reasonable
Proportion of <i>EGFR</i> -positive NSCLC patients with Ex20ins	8.96%	Moore 2018	Reasonable The ESC agreed with the evaluation that, although the revised estimate is at the higher end of the range noted by DUSC (see Table 2), it can be considered reliable as the study used a more robust testing method which remains important in this regard.
Proportion with ECOG performance status of 0-2	80.1%	Mitchell 2013	Reasonable
Proportion who elect 1L PBC	85%	Table 2, PD-L1 Stakeholder Meeting, Feb 2019	Reasonable
Proportion who progress following 1L PBC	70%	Expert opinion from the clinical advisory board	Reasonable
Prevalent cases	81	1.31 years (duration of illness since diagnosis of advanced disease in Study 101) x incident population in previous years	Reasonable

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Data	Value	Source	Comment
Utilisation			
Uptake of mobocertinib	█%	Assumption The November 2022 submission had assumed a █% uptake in Years 1 and 2, increasing to █% in Year 3 and onward.	This is an area of uncertainty. However, a high uptake rate of mobocertinib is expected if the risk-benefit balance of mobocertinib is favourable in clinical practice.
Treatment duration of mobocertinib	Mean duration (cycles) in each treatment year: 1 st treatment year: 7.94 cycles 2 nd treatment year: 2.93 cycles 3 rd treatment year: 1.29 cycles 4 th treatment year: 0.43 cycles 5 th treatment year: 0.15 cycles 6 th treatment year: 0.05 cycles	Based on modelled TTD (Study 101)	Reasonable
Distribution of standard of care treatments in current clinical practice	Docetaxel: 21.8% Gemcitabine: 8.2% Pemetrexed: 45.4% Carboplatin: 22.7% Paclitaxel: 1.8%	Pooled data from Study 5008 and Study 5002	Reasonable
Treatment duration for standard of care	Mean duration (cycles) in each treatment year: 1 st treatment year: 4.41 cycles 2 nd treatment year: 0.86 cycles 3 rd treatment year onward: 0 cycle	Based on modelled TTD (pooled data from Study 5002 and 5008)	Reasonable
Relative dose intensity	93% - for both mobocertinib and standard of care	Study 101	Reasonable
Drug costs			
Mobocertinib	Effective DPMQ of \$█	Proposed effective price	Appropriate
Standard of care	Weighted dispensed price for each item based on the public/private split	Published price	Reasonable data source. Resubmission considered only the costs of chemotherapy which is appropriate.
PBS/RPBS services & co-payment			
PBS/RPBS services split Public/Private split	Variable by treatment class	PBS/RPBS items for nominated basket of 2L therapies:	Reasonable

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Data	Value	Source	Comment
Weighted average co-payment		Jan 2021 to Dec 2021	
Medical services			
Parenteral administration of antineoplastic agents	100% Schedule fee: \$114.20 (80% rebate used in the financial analysis)	MBS item 13950	Appropriate

Source: Based on Table 4-1, p232 of the first submission and Table 4-1, p 25 of the resubmission.

AIHW = Australian Institute of Health and Welfare; DPMA = dispensed price for maximum amount ; DPMQ = dispensed price for maximum quantity; DUSC = Drug Utilisation Sub-Committee; ECOG = Eastern Cooperative Oncology Group; EGFR = epidermal growth factor receptor; Exon20ins = exon 20 insertions; MSAC = Medical Services Advisory Committee; NCCI = National Cancer Control Indicators; NSCLC = non-small cell lung cancer; PBC = platinum-based chemotherapy; PBS = Pharmaceutical Benefits Schedule; PSD = public summary document; RPBS = Repatriation Pharmaceutical Benefits Scheme

Blue shading indicates components remaining unchanged since the previous submission.

6.55 The estimated use and financial impacts of listing mobocertinib are summarised in Table 15.

Table 15: Estimated use and financial implications

	2024	2025	2026	2027	2028	2029
Estimated extent of use						
Number of patients initiating treatment with mobocertinib	1	1	1	1	1	1
Total number of patients treated	1	1	1	1	1	1
Number of scripts dispensed ^a	2	2	2	2	2	2
Previous submission (November 2022)						
Number of patients initiating mobocertinib treatment	1	1	1	1	1	1
Total treated patients	1	1	1	1	1	1
Number of scripts dispensed ^a	2	2	2	2	2	2
Estimated financial implications of mobocertinib						
Cost to PBS/RPBS less copayments	3	3	3	3	3	3
Estimated financial implications for chemotherapy						
Cost to PBS/RPBS less copayments	3	3	3	3	3	3
Net financial implications						
Net cost to PBS/RPBS	3	3	3	3	3	3
Net cost to MBS	4	4	4	4	4	4
Net cost to PBS/RPBS/MBS	3	3	3	3	3	3
Net cost to PBS/RPBS/MBS (Revised) ^b	3	3	3	3	3	3
Previous submission (November 2022)						
Net cost to PBS/RPBS	3	3	3	3	3	3

Source: Table 4-6 p30, Table 4-7 p30, Table 4-8 p31, Table 4-9 p31, Table 4-10 of the resubmission.

^a For incident patients, the number of scripts was estimated to be 7.38 in the first year of treatment, 2.73 in the second year, 1.21 in the third year, 0.40 in the fourth year, 0.14 in the fifth year and 0.05 in the sixth year. This has taken into account the treatment duration in each treatment year and the relative dose intensity (93%).

^b After correcting for the calculation errors and applying TTD specific to chemotherapy population

Blue shading indicates information previously seen by the PBAC.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5000

³ \$0 to < \$10 million

⁴ net cost saving

- 6.56 The total cost to the PBS/RPBS of listing mobocertinib was estimated to be \$0 to < \$10 million in Year 6, and a total of \$10 million to < \$20 million in the first 6 years of listing.

Quality Use of Medicines

- 6.57 In the previous submission, the Sponsor proposed that educational materials will be developed and made available for treating clinicians and patients should mobocertinib be approved for funding on the PBS for the proposed indication.

Financial Management – Risk Sharing Arrangements

- 6.58 The resubmission did not propose any risk-sharing arrangement.

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

7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule Authority Required listing of mobocertinib for the treatment of adults with locally advanced (Stage IIIB/IIIC) or metastatic (Stage IV) non-small cell lung cancer (NSCLC) harbouring epidermal growth factor receptor exon 20 insertion (*EGFR* ex20ins) mutations whose disease has progressed on or after platinum-based chemotherapy (PBC). The PBAC was satisfied that mobocertinib provides, for some patients, a significant improvement in efficacy over standard of care (SOC). The PBAC considered the amendments made in the resubmission, including changes to the economic model, a reduced price and revised financial estimates had sufficiently addressed the Committee's previous concerns.
- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of mobocertinib would be acceptable at the price proposed in the submission.
- 7.3 The PBAC noted the input from individuals, health care professionals, Lung Foundation Australia and Rare Cancers Australia supported the clinical need for additional effective treatment options for this population, given that patients have a poor prognosis and there is currently no listed therapy that targets the *EGFR* ex20ins mutation. In addition, the PBAC noted the Medical Oncology Group of Australia's support for the submission.
- 7.4 The PBAC noted that the proposed restrictions in the resubmission incorporated all changes suggested by the Committee at its November 2022 meeting (see paragraph 3.2). In addition, the PBAC considered it would be appropriate to remove the reference to histology in the restriction to allow patients with squamous cell NSCLC to access treatment due to their inclusion within the trial used as evidence in the submission (see paragraph 3.3).
- 7.5 The PBAC noted that the resubmission nominated chemotherapy as the comparator but did not limit it to taxanes due to the limited available evidence (see paragraph 5.3). The PBAC agreed with the ESC that the use of multiple forms of chemotherapy in

this context was reasonable as the nominated comparator. The PBAC also noted the comparator for the clinical claim remained the same as the November 2022 submission (i.e. SOC comprising standard *EGFR* tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitor (ICI) monotherapy, and chemotherapy). The PBAC recalled concerns regarding use of TKIs and ICIs in this context and noted the Pre-Sub-Committee response and pre-PBAC response provided some evidence of ICI use in this patient population (see paragraph 5.2).

- 7.6 The PBAC recalled that in November 2022 it had acknowledged that mobocertinib may be better than conventional chemotherapy in this setting, but it did not consider that the November submission had adequately demonstrated this in terms of the evidence presented against SOC, where the majority of SOC treatments in Studies 5008 and 5002 comprised *EGFR* TKIs and ICI monotherapy, not chemotherapy (para 7.6, mobocertinib, PSD, November 2022 PBAC meeting). At that time the PBAC had advised that a resubmission should include a clinical analysis that measured an incremental benefit for mobocertinib compared with chemotherapy-based treatments (para 7.11, mobocertinib, PSD, November 2022 PBAC meeting). The PBAC noted the resubmission presented an indirect treatment comparison (ITC) of the mobocertinib pooled prior platinum (PPP) cohort from Study 101 (N=114) *versus* the pooled chemotherapy cohort from studies 5002 and 5008 (N=23), as requested. The resubmission also presented an ITC of the mobocertinib PPP cohort from Study 101 *versus* the pooled chemotherapy cohort from Studies 5002 and 5008, as requested by the PBAC. The PBAC noted the limitations of the ITCs presented (see paragraph 6.32). The PBAC agreed with the ESC, that the data presented were associated with a high risk of bias resulting in uncertainty around the magnitude of the comparative treatment benefits for mobocertinib *versus* chemotherapy or *versus* SOC. However, despite the data limitations, the PBAC considered the requested provision of a comparison with chemotherapy provided additional support to the claim of superior effectiveness. As such, the PBAC considered the claim of superior effectiveness compared to SOC was uncertain but likely reasonable in this a rare subset of *EGFR* mutations.
- 7.7 The PBAC considered that the claim that mobocertinib has a different safety profile compared to chemotherapy or immunotherapy and that its safety profile is acceptable and similar to that of other TKIs was reasonable.
- 7.8 The PBAC noted the resubmission provided an economic analysis that included the use of pooled Kaplan-Meier (KM) data from studies 5002 and 5008, the application of only chemotherapy costs for comparator and subsequent treatments and a revised proposed price of mobocertinib (see paragraph 3.1). The resulting resubmission base case incremental cost-effectiveness ratio (ICER) was \$55,000 to < \$75,000 per quality-adjusted life years (QALYs) gained. The PBAC noted it had previously recommended other targeted therapies for the second line treatment of NSCLC with ICERs of \$45,000 to \$75,000 per QALY gained (para 7.9, mobocertinib, PSD, November 2022 PBAC meeting). The PBAC noted the pooled KM data from studies 5002 and 5008 used in

the model was not restricted to chemotherapy survival data. The PBAC acknowledged the concerns raised by the ESC that the use in the model of survival estimates from pooled SOC favoured mobocertinib. However, the PBAC considered the small sample size of the pooled chemotherapy cohort from Studies 5002 and 5008 (N=23) increased the uncertainty with the survival estimates and agreed with the resubmission that use of pooled SOC data in the economic model was reasonable. The PBAC advised that the revised economic analysis and price proposed in the resubmission addressed previous concerns regarding the cost-effectiveness of mobocertinib.

- 7.9 The PBAC recalled that in November 2022, it had considered that a resubmission for mobocertinib should present revised financial estimates consistent with the DUSC advice for the proportion of patients with Stage IIIB/IV NSCLC, the prevalence of *EGFR* ex20ins and the number of prevalent patients (para 6.81, Mobocertinib PSD, November 2022 PBAC meeting). In addition, the PBAC recalled that in November 2022 it had advised that the revised financial implications should exclude the use of *EGFR* TKIs and ICI monotherapy financial offsets. The PBAC considered the resubmission appropriately considered only the costs of chemotherapy in the financial offsets and addressed the concerns raised by DUSC. The PBAC accepted the revised financial estimates.
- 7.10 With respect to flow on changes to other restrictions the PBAC noted that gefitinib, erlotinib and afatinib are *EGFR* TKIs that are currently listed for Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC. The initial treatment restrictions for these items currently contain a clinical criterion that restricts sequential use of *EGFR* TKIs. The clinical criteria states 'Patient must not have received previous PBS-subsidised treatment with another *EGFR* TKI' with an exception being in patients who have developed intolerance of a severity necessitating permanent treatment withdrawal. However, gefitinib, erlotinib and afatinib are *EGFR* TKIs to which ex20ins variants are typically insensitive. As such, the PBAC considered that, with the listing of mobocertinib, patients with an ex20ins mutation should be excluded from the Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC restrictions for gefitinib, erlotinib and afatinib.
- 7.11 The PBAC recommended that mobocertinib should not be treated as interchangeable with any other drugs.
- 7.12 The PBAC advised that mobocertinib is not suitable for prescribing by nurse practitioners.
- 7.13 The PBAC recommended that the Early Supply Rule should not apply.
- 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 mobocertinib:
- a) Due to the limitations of the available evidence, the PBAC considered the

magnitude of the comparative treatment benefits for mobocertinib was uncertain and hence the criteria of providing a substantial and clinically relevant improvement in efficacy was not met;

- b) The treatment is not expected to address a high and urgent unmet clinical need due to the availability of alternative therapies (see paragraph 4.3);
- 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 noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
MOBOCERTINIB mobocertinib 40 mg capsule, 112	NEW	1	112	5	EXKIVITY
		<i>Max.qty (packs) multiplier = 1 Repeat increases: nil</i>			
Concept ID	Category / Program: GENERAL – General Schedule (Code GE)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners				
	Restriction Type <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)				
	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.				
	Indication: Stage IIIB or IIIC (locally advanced) or IV (metastatic) non-small cell lung cancer (NSCLC)				
	Treatment Phase: Initial PBS-subsidised treatment				
	Clinical criteria				
	The treatment must be the sole PBS-subsidised therapy for this condition				
	AND				
	Clinical criteria				
	Patient must have/have had a WHO performance status of 2 or less prior to initiation of treatment with this drug for this condition				
	AND				
	Clinical criteria				
	Patient must not have previously received this drug for this condition; OR				

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	Patient must be each of: (i) currently receiving non-PBS subsidised supply for this drug for this PBS indication, (ii) untreated with this drug at the time that non-PBS subsidised supply was commenced, (iii) free of disease progression since commencing non-PBS subsidised supply
	AND
	Clinical criteria
	Patient must have/have had progressive disease following platinum-based chemotherapy
	AND
	Clinical criteria
	Patient must have evidence in tumour material of an activating epidermal growth factor receptor (<i>EGFR</i>) exon 20 insertion mutation
	Administrative Advice: A patient may only qualify for PBS-subsidised treatment under this restriction once. Following completion of the initial PBS-subsidised course, further applications for treatment will be assessed under the continuing treatment restriction.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
	Restriction Type <input checked="" type="checkbox"/> Authority Required – immediate/real time assessment by Services Australia (telephone/online application avenues)
	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.
	Indication: Stage IIIB or IIIC (locally advanced) or IV (metastatic) non-small cell lung cancer (NSCLC).
	Treatment Phase: Continuing
	Clinical criteria
	The treatment must be the sole PBS-subsidised 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 have developed disease progression while receiving treatment with this drug for this condition
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 888 333.

Flow on changes:

- 8.2 Amend the gefitinib (8769M), erlotinib (25 mg 10022L and 11263T, 100 mg 10020J and 11260P, 150 mg 10014C and 11259) and afatinib (20 mg 11335N and 11336P, 30 mg 11341X and 11348G, 40 mg 11359W and 11347F, 50 mg 11329G and 11342Y) for Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC listings as follows:

	Population criteria:
	Patient must have evidence of an activating epidermal growth factor receptor (<i>EGFR</i>) gene mutation known to confer sensitivity to treatment with <i>EGFR</i> tyrosine kinase inhibitors in tumour material; AND
	Population criteria:
	<i>Patient must not have evidence in tumour material of an activating epidermal growth factor receptor (EGFR) exon 20 insertion mutation</i>

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

The sponsor had no comment.