TAR 436A – Immune checkpoint inhibitors for metastatic non-small cell lung cancer

Purpose of this TAR

This Technology Assessment Report (TAR) is an update to TAR 436. Results and methodological updates described in this TAR supersede those reported in TAR 436. However, the majority of the key evidence, assumptions and analysis are reported in the earlier TAR and remain unchanged unless stated otherwise in this TAR. The reader should therefore familiarise themselves with TAR 436 before reading this update.

Pharmac has received several applications for the funding of immune checkpoint inhibitors (ICIs) for first-line (1L) or second-line (2L) use in patients with metastatic, non-small cell lung cancer (NSCLC) with the Epidermal Growth Factor Receptor (EGFR) Anaplastic Lymphoma Kinase Positive (ALK+) wildtype, gene. The individual agents, the ICI class and each line of therapy have been reviewed by PTAC and CTAC (previously referred to as CaTSoP) on several occasions, as detailed in TAR 436 and the records of the clinical advice meetings at which those reviews took place. At the time of writing, there were three agents (pembrolizumab, nivolumab and atezolizumab) with positive clinical advice recommendations for use in in this indication.

In March 2022, Pharmac staff drafted a memo (Stage IV NSCLC CTAC memo) seeking additional advice at the CTAC April 2022 meeting. The purpose of the memo was to seek updated input and confirmation that CTAC's prior advice remains current, given that the last advice received was in 2020 and that there are ongoing changes expected across the health system. In addition, updated, longer-term survival data were provided for selected agents. This TAR presents the changes made since the analysis described in TAR 436, based on advice received at the April meeting.

On 6 July 2022, Pharmac released a request for proposal (RFP) for the supply of ICIs for the treatment of NSCLC. This TAR also reports changes made to the cost-effectiveness and budget impact estimates based on the bids received from suppliers and additional clinical advice received in light of proposals for new agents received as part of the RFP process.

A summary of the ICIs considered is provided in the tables below.

PROPOSAL OVERVIEW	
Pharmaceutical	Atezolizumab (Tecentriq)
Supplier	Roche
Proposed Indication	• 1L monotherapy PD-1/PDL-1 expression ≥50% • 1L combination therapy with bevacizumab and platinum-based chemotherapy • 2L monotherapy
Dosing	• 840mg, 2-weekly • 1200mg, 3-weekly • 1680mg, 4-weekly
Pharmaceutical Price	1200mg vial: $9,503 gross, S 9(2)(b)(ii), net, S 9(2) net per mg. Commercial offer received June 2020 (Objective ID A1361252)
PTAC PRIORITY	1L monotherapy PD-1 expression >50% • High – CaTSoP July 2020 • Noted previous recommendation. – CTAC April 2022 1L combination therapy • Decline - CaTSoP April 2019 due to insufficient evidence for this combination. • Decline – CaTSoP July 2020 • Decline - CTAC April 2022 2L monotherapy • No rec. - PTAC Feb 2016 • Low - PTAC Aug 2017 • Low - CaTSoP Aug 2017 • Noted previous recommendation - CTAC April 2022
Pharmconnect	• 1L monotherapy (P-001521) • 1L combination therapy (P-000836) • 2L monotherapy (P-000243) Related bundle proposals • Bundle - Immune Checkpoint Inhibitors – Metastatic NSCLC, 1L monotherapy (PD-L1 >50%), 1L combination therapy (all-comers), 2L monotherapy (all-comers). Note that this bundle does not specify the treatment line in which atezolizumab is indicated

PROPOSAL OVERVIEW	
Pharmaceutical	Nivolumab (OPDIVO)
Supplier	Bristol-Myers Squibb (BMS)
Proposed Indication	2L monotherapy
Dosing	• 240mg, 2-weekly • 360mg. 3 weekly • 480mg, 4-weekly
Pharmaceutical Price	40mg vial: $1,051.98 gross, S 9(2)(b) net, S 9(2)(b) net per mg 100mg vial: $2,629.96 gross, S 9(2)(b)(ii), net, S 9(2)(b) net per mg Pharmac contract 2016 (Objective ID A901169)
PTAC Priority	2L monotherapy • No formal recommendation. - PTAC Feb 2016 • Low-Med - CaTSoP April 2016 • Low - PTAC May 2016 • Noted previous recommendation. - CTAC April 2022
PHARMConnect	• 2L monotherapy (P-000793) • 2L monotherapy squamous (P-000598) Related bundle proposals • Bundle - Immune Checkpoint Inhibitors – Metastatic NSCLC, 1L monotherapy (PD-L1 >50%), 1L combination therapy (all-comers), 2L monotherapy (all-comers). Note that this bundle does not specify the treatment line in which atezolizumab is indicated

PROPOSAL OVERVIEW	
Pharmaceutical	Pembrolizumab (Keytruda)
Supplier	Merck Sharp & Dohme (MSD)
Proposed Indication	• 1L monotherapy PD-1 expression ≥50% • 1L combination therapy: • 2L monotherapy
Dosing	• 200mg, 3-weekly, • 400mg, 6-weekly
Pharmaceutical Price	100mg vial: $4,680 gross, S 9(2)(b)(ii), net, S 9(2)(b) net per mg.
PTAC Priority	1L monotherapy PD-1 expression >50% • Low –CaTSoP Mar 2017 • Defer –PTAC May 2017 pending mature data & PD-L1 biomarker information • No formal recommendation – PTAC Nov 2017, Aug 2018 • Med – PTAC Nov 2018 • Med – PTAC Feb 2019 • High – CaTSoP April 2019 • Noted previous recommendation– CTAC April 2022 1L combination therapy • Med – PTAC Nov 2018 • Noted previous recommendation – PTAC Feb 2019 • Noted previous recommendation – CTAC April 2022 2L monotherapy • Low - PTAC Nov 2016 • Low – CaTSoP Mar 2017 • No formal recommendation – PTAC Aug 2017 • Noted previous recommendation– CTAC April 2022
PHARMConnect	• 1L monotherapy • 1L combination therapy • 2L monotherapy Related bundle proposals • Bundle - Immune Checkpoint Inhibitors – Metastatic NSCLC, 1L monotherapy (PD-L1 >50%), 1L combination therapy (all-comers), 2L monotherapy (all-comers). Note that this bundle does not specify the treatment line in which atezolizumab is indicated

Executive Summary

The cost-effectiveness of immune checkpoint inhibitors (ICIs) for the treatment of metastatic non-small cell lung cancer (NSCLC) has previously been estimated in TAR 436 (Objective ID A1461122), with cost-effectiveness estimates varying from S 9(2)(b)(ii) to S 9(2)(b)(ii), 9 QALYs per $m invested, depending on the specific funding proposal. This TAR (436A) reflects the following amendments:

- Narrowing of the list of proposals to two feasible funding scenarios:
  - **Funding Scenario A**: 1L monotherapy for patients with PDL-1 > 50% plus 1L combination therapy for all-comers and 2L monotherapy for all-comers.
  - **Funding Scenario B**: 2L monotherapy for all-comers.
- Updated clinical parameters in light of new trial evidence
- Updated dosing regimens to better reflect potential clinical practice in NZ.
- Inclusion of hospitalisation costs for all patients
- Updated patient numbers reflecting the feasible funding scenarios, patients currently receiving systemic therapy and likely uptake following the funding of an ICI

As a result of these changes, the cost-effectiveness range for ICIs for metastatic NSCLC is now estimated to be:

- Funding Scenario A: S 9(2)(b)(ii), 9 **QALYs** per $m
- Funding Scenario B: S 9(2)(b)(ii), 9 **QALYs** per $m

The BIA has also been updated, with the 5-year NPV to the pharmaceutical budget of S 9(2)(b)(ii), 9(2)(ba)(i) & and S 9(2)(b)(ii), 9(2) for Funding Scenarios A and B, respectively. The overall net impact to the health sector (5-year NPV) is estimated to be S 9(2)(b)(ii), 9(2)(ba)(i) & for Funding Scenario A and S 9(2)(b)(ii), 9(2) for Funding Scenario B.

This TAR also reports changes made to the cost-effectiveness and budget impact estimates based on the bids received from suppliers and additional clinical advice received in light of proposals for new agents received as part of the RFP process. It should be noted that the RFP results reflect the most up to date cost-effectiveness and budget impact results.

1. Proposal Overview

1.1 Summary

Advice received in the CTAC April 2022 meeting was that:

- PDL-1 expression greater than 50% (PDL-1 > 50%), as ascertained by a PDL-1 test, should be required for patients to access ICI monotherapy: *"The Committee considered testing should be mandated in this line of therapy in order to access monotherapy. The Committee considered access without confirmation of PD-L1 expression in this patient population may result in a proportion of patients receiving futile therapy with significant cost to the sector"*
- There are likely to be patients who are unable to undergo invasive testing, and that ICI therapy should be available to these patients. The Committee considered that *"access to ICI's in 1L combination therapy and 2L therapy without PD-L1 testing would reasonably accommodate for this and reduce the impact on lab testing for PD-L1 testing upon listing of any agent, giving time to develop the systems required to support reflex PD-L1 testing within New Zealand."*

In light of this advice, two funding scenarios were considered to be feasible.

1. **Funding Scenario A**: 1L monotherapy for patients with PDL-1 expression > 50% plus 1L combination therapy for all-comers and 2L monotherapy for all-comers. The population, intervention, comparator and outcomes (PICO) details for this scenario are presented in Table 1
2. **Funding Scenario B**: 2L monotherapy for all-comers. The PICO details for this scenario are presented in Table 2.

Table 1: PICO for Funding Scenario A

PICO	
POPULATION	Patients with EGFR-wildtype, locally advanced or metastatic non-small cell lung cancer who have not yet received any treatment for their metastatic disease
INTERVENTION	**1L, PDL-1 > 50%** 1L: ICI 2L: Platinum based chemotherapy 3L: Docetaxel **1L, All-comers** 1L: ICI in combination with platinum-based chemotherapy 2L: Docetaxel **2L, All-comers** 2L: ICI 3L: Docetaxel
COMPARISON	**1L (both monotherapy and combination therapy)** 1L: Platinum based chemotherapy 2L: Docetaxel

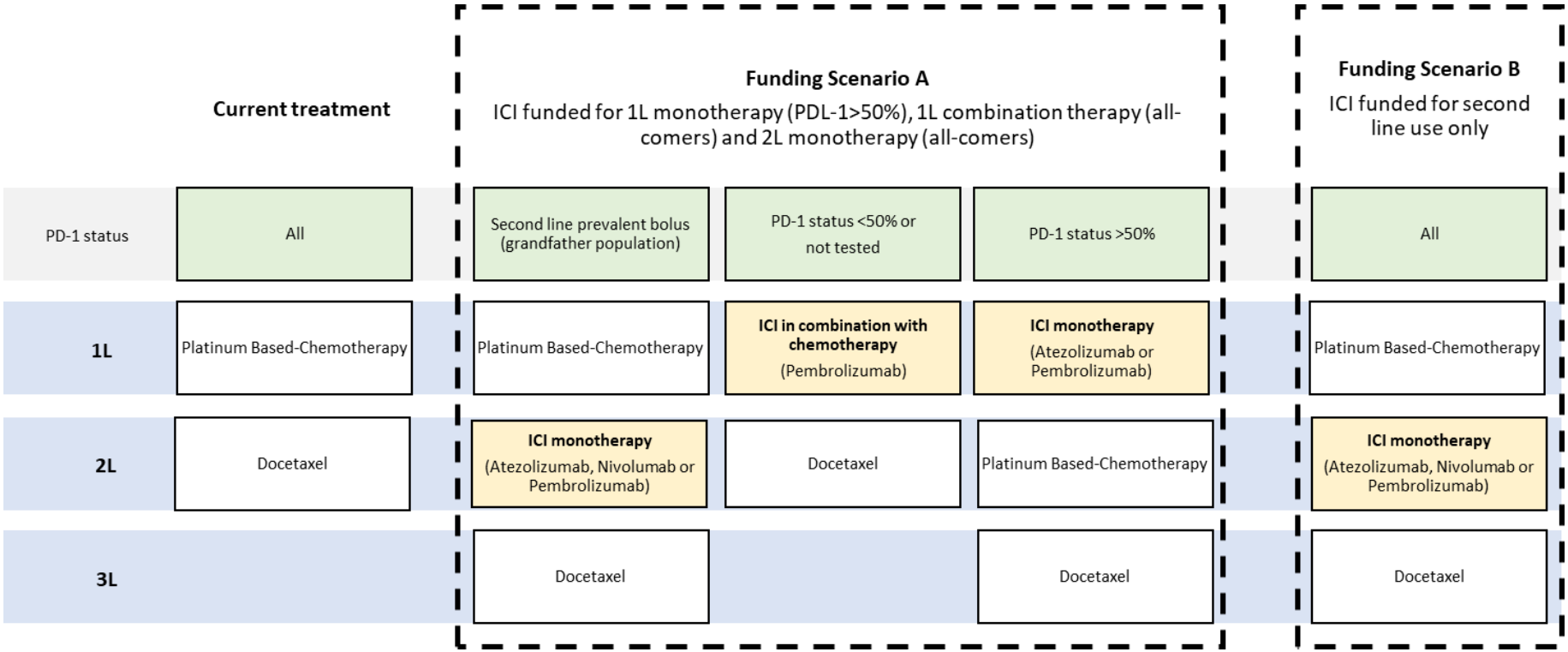
	2L 2L: Docetaxel 3L: BSC
OUTCOME	Improvement in the time to disease progression (improvement in progression free survival (PFS)) and time to death (improvement in overall survival (OS))

Table 2: PICO for Funding Scenario B

PICO	
POPULATION	Patients with EGFR-wildtype, locally advanced or metastatic non-small cell lung cancer who have progressed following 1L ttreatment for their metastatic disease.
INTERVENTION	2L: ICI 3L: Docetaxel
COMPARISON	2L: Docetaxel 3L: BSC
OUTCOME	Improvement in the time to disease progression (improvement in progression free survival (PFS)) and time to death (improvement in overall survival (OS))

Scenarios A and B are depicted in Figure 1. For an overview of the funding scenarios proposed and assessed prior to this meeting, please see Figure 2 in TAR 436.

Figure 1: Funding Scenarios



2 Health Benefits

2.1 Review of Clinical Evidence

The pivotal clinical evidence for ICI treatment in NSCLC is summarised in the Health Benefits section in TAR 436. Updated, longer-term survival evidence is also summarised in the Clinical Evidence section of the Stage IV NSCLC CTAC memorandum (Objective ID A1571084), which was sent to CTAC by Pharmac staff ahead of the April 2022 meeting.

3 PHARMAC Cost-Utility Analysis

The cost-utility analysis undertaken to estimate the cost-effectiveness of ICIs for NSCLC in Scenarios A and B is the same as that described in TAR 436, with the exception of amendments made to the following model components, which are described in the sections below.

- Overall model changes to reflect updated funding scenarios (Scenarios A and B described in section 1.1)
- Updated overall survival (OS) and progression free survival (PFS) data using five-year outcomes from the KEYNOTE-024 follow up study (Reck et al., J Clin Onc. 2021: 39(21).)
- Pembrolizumab dosing regimen
- Health sector utilisation

A summary of the changes made is presented in Table 3. The changes are described in more detail below.

Table 3: Summary of updates from TAR 436 analysis

Update	TAR 436 (Prior TAR)	TAR 436A (Update)
Pembrolizumab monotherapy OS and PFS	• From Reck et al., J Clin Oncol. 2019; 1;37(7). (OS) and Reck et al., N Engl J Med. 2016; 10;375(19) (PFS) • Median OS was 30 months and median PFS was 10.3 months	• From Reck et al. 2021 • Median OS was 26.3 months and median PFS was 7.7 months
Pembrolizumab dosing regimen	• People receive 3-weekly dosing for the entire treatment course	• Based on CTAC advice, people receive 3-weekly dosing initially • From month 6 onwards, dosing is 6-weekly
Health sector utilisation	• No wider health sector costs were included	• Hospitalisation costs of $259 (1L) and $195 (2L) per week added to the model

The overall impact of these results is to marginally reduce the cost-effectiveness of each scenario:

- The cost-effectiveness of Funding Scenario A is now estimated to be S 9(2) (b)(ii) 9 QALYs per $m, while the most comparable scenario in the previous analysis, Proposal E, was estimated to be S 9(2) (b)(ii) 9.
- The cost-effectiveness of Funding Scenario B is now estimated to be S 9(2) (b)(ii) 9 QALYs per $m, while in the previous analysis it was estimated to be S 9(2) (b)(ii) 9.

Updated OS and PFS from KEYNOTE-024 follow-up

Updated/long-term follow up OS and PFS evidence from Reck et al., 2021 (pembrolizumab monotherapy) and Jassem, J et al. J Thorac Oncol. 2021;16(11) (IMPOWER 110 trial for atezolizumab monotherapy) were presented in the Stage IV NSCLC CTAC memorandum sent to CTAC ahead of the April 2022 meeting. In that memorandum, Pharmac sought advice based on the new evidence, on:

- Whether the Committee still considered it appropriate to assume that atezolizumab and pembrolizumab 1L monotherapy provide the same or similar treatment benefit (i.e., a class effect)
- Whether the Committee's earlier recommendations remain appropriate

In the CTAC April 2022 meeting, the Committee considered that it remained appropriate to assume that pembrolizumab and atezolizumab provide equivalent treatment benefit for 1L NSCLC monotherapy, and that it was also reasonable to assume equivalent benefit could be achieved by all three agents (pembrolizumab, atezolizumab and nivolumab) when funded as 2Lmonotherapy. The Committee did not change or withdraw any of its prior recommendations.

Given this advice, the updated PFS and OS data from the KEYNOTE-024 follow-up (Reck et al. 2021) were used to update the transition probabilities for 1L monotherapy. Figure 2 and Figure 3 show the updated OS and PFS curves, respectively.

Figure 2: Updated Kaplan-Meier OS curve (% alive by month) – Pembrolizumab monotherapy (KEYNOTE-024 follow-up) [Figure 2A Reck et al. 2021]

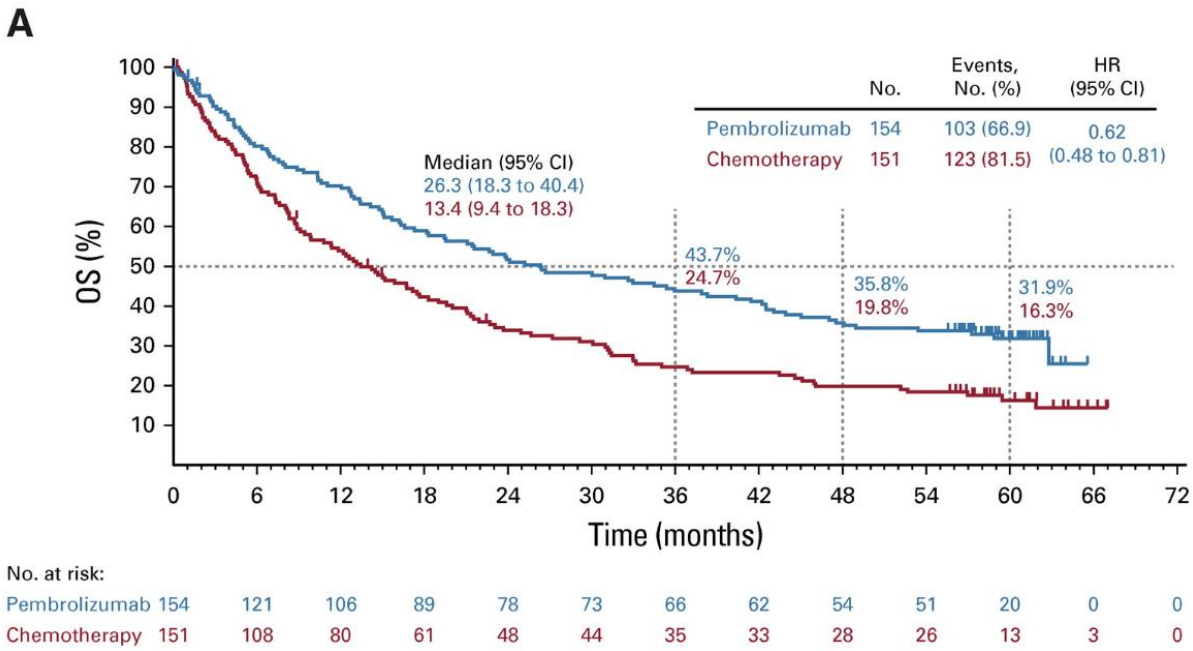
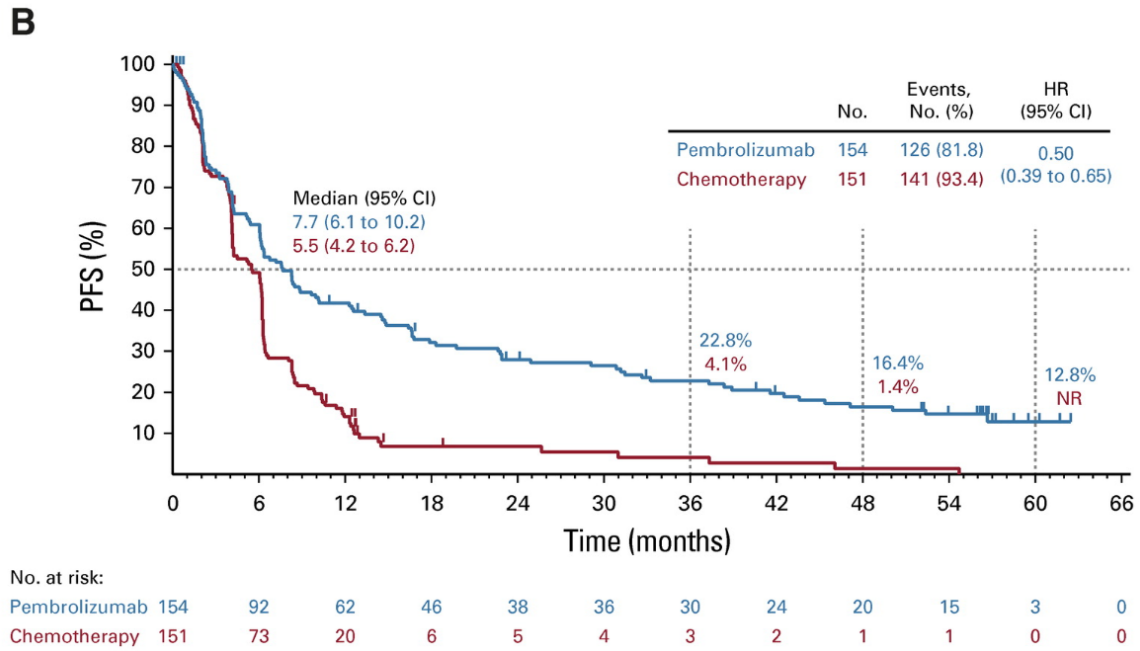


Figure 3: Update Kaplan-Meier PFS curve (% without disease progression by month) – Pembrolizumab monotherapy (KEYNOTE-024 follow-up) [Figure 2B Reck et al. 2021]



These curves were then plot-digitised and fitted with exponential and log normal curves to extrapolate beyond trial follow up. The log-normal distribution had a better fit, with R-squared values of 0.987 and 0.963 for OS and PFS, respectively. Figure 4 shows the log-normal curve fitted to the OS Kaplan-Meier data, and Figure 5 shows the log-normal curve

fitted to the digitised PFS Kaplan-Meier data. The log-normal function defined to approximate the OS curve is defined by a mean, μ, of 3.3 and a standard deviation, σ, of 1.7. The parameters μ and σ that define the function used to approximate the PFS curve are 2.15 and 1.7, respectively.

Figure 4: Log-normal curve overlaid on digitised Kaplan-Meier OS data

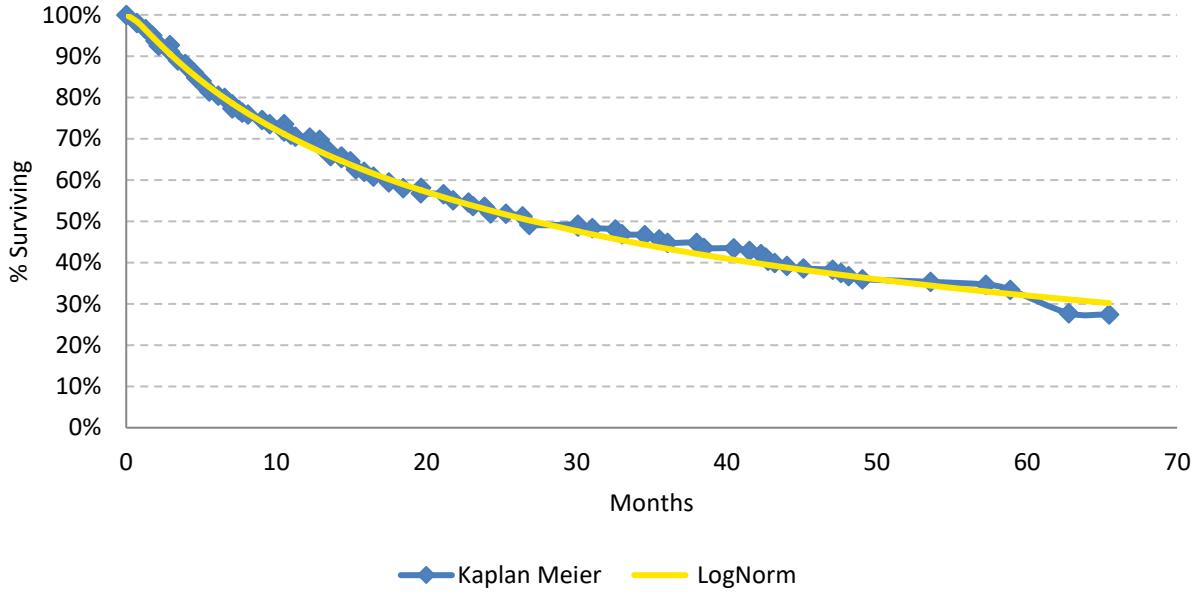
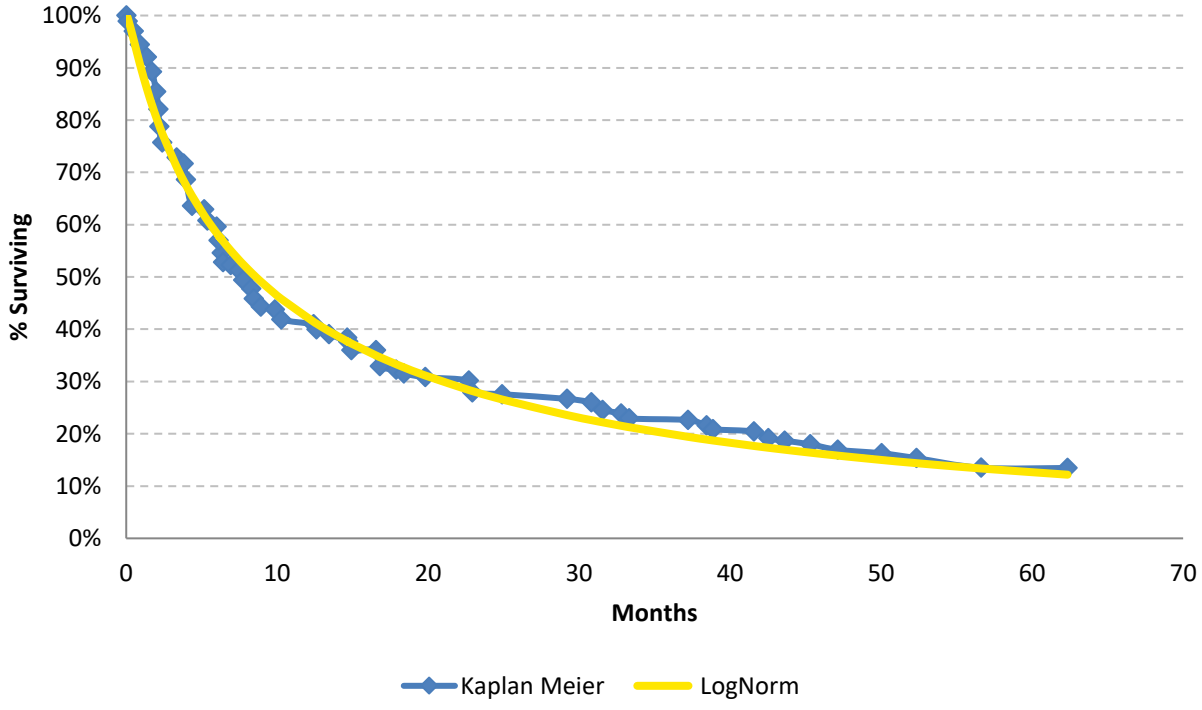


Figure 5: Log-normal overlaid on digitised Kaplan-Meier PFS data



Using the log-normal OS curve presented above, the probability of death was estimated as defined in Equation 1, with P(survival)$_t$ approximated based on the log-normal curve function at each time point t.

Equation 1. Probability of death at a given month

$$\mathrm{P}\,(Death)_t = 1 - \frac{\mathrm{P}\,(survival)_t}{\mathrm{P}\,(survial)_{t-1}}$$

The probability of progression was estimated in the same way using the PFS curve.

Finally, the monthly probabilities were converted into weekly probabilities to align with the model cycle length, using the 'probtoprob' function in TreeAge.

Pembrolizumab dosing regimen

Both 3-weekly and 6-weekly dosing of pembrolizumab have been approved by MedSafe\ (Medsafe pembrolizumab datasheet). In the Stage IV NSCLC CTAC memorandum, Pharmac sought clarification on the proportion of patients who took up pembrolizumab who were likely to receive each dosing regimen, and whether patients were likely to start on one regimen and transition to the other over time.

In the CTAC April 2022 meeting, the Committee noted that: *"The proportion of patients treated with 3-weekly versus 6-weekly dosing is unknown, and that this would depend on pressures on day-units/infusion services, or if the patients live rurally. The Committee noted that it is likely that clinicians would have a 6-9 month cut-off with dosing 3-weekly to ensure patients will respond and are not experiencing significant toxicities. The Committee considered that then patients may be moved to 6-weekly dosing. The Committee noted, however, that there is no evidence to underpin these assumptions*."

To reflect this advice, as well as the high pressure on infusion services at present, pembrolizumab dosing in the model was assumed to be 3-weekly for the first 5 months, and 6-weekly from 6-months onwards.

Hospitalisation costs

As part of this update, the cost of inpatient hospitalisations and inpatient stays were included in the CUA. Prior to this update, no health sector costs outside of those relating to treatment were included in the CUA. Even though these costs are not linked to treatment, effective treatments that result in longer survival for patients would result in greater health sector utilisation (including hospitalisations) and therefore higher health sector costs, so it is important to capture these costs in the economic modelling.

Health sector utilisation data was sourced from the PIvoTAL study (Lee et al., BMC Health Services Research, 2018: 18:147). The study retrospectively looked at the real-world health utilisation data of patients with advanced or metastatic NSCLC across 9

countries globally. The study included 1,440 patients of whom 208 were from Australia. The key results from the Australian cohort were:

- The number of hospitalisations per 100 patient weeks was 4.83 in the 1L and 3.63 in the 2L setting
- The number of emergency department (ED) admissions per 100 patient weeks was 1.24 in the 1L and 1.25 in the 2L setting

In the NSCLC CTAC memo, Pharmac sought advice on whether the health sector utilisation data reported by Lee et al. is representative of NSCLC resource utilisation in New Zealand. The Committee's advice was that the utilisation data for the cohort of patients from Australia was broadly representative of utilisation in New Zealand, but that this study was undertaken in a setting where ICI treatments were available.

In response to this advice, Pharmac added the cost of hospitalisation to both the 1L and 2L models. No treatment-specific difference in the cost of hospitalisations per week was included, since hospitalisation data stratified by treatment were not provided. No ED costs were included since they were negligible in comparison to the hospitalisation costs.

The average cost of an NSCLC hospitalisation was estimated by multiplying the cost of each relevant DRG codes by the proportion of total discharges coded E71A, B or C that each code made up. The average cost of an NSCLC hospitalisation was estimated to be $5,359. This calculation is presented in Table 4 below.

Table 4: Weighted average cost of a NSCLC hospitalisation

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

*WIESNZ21 cost weights; Pharmac CUA cost spreadsheet

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

- The average cost per hospitalisation was then multiplied by the hospitalisations per 100 weeks data from Lee et al.:
    - 1L: 4.83 * $5,359 = $25,882

- 2L: 3.63 * $5,359 = $19,452

- Finally, the costs per 100 weeks were divided by 100 to get a weekly cost, which aligns to the model cycle length. For 1L, the weekly cost is $259, while for 2L it is $195. These costs were then applied each cycle, to all living patients in both the 1L and 2L models, regardless of health state.

3.1 Cost-Effectiveness Results

Funding Scenario A: 1L monotherapy PDL-1 > 50%, 1L combination therapy (all-comers), 2L monotherapy (all-comers)

The base case values for pharmaceutical price and clinical effectiveness parameters for Funding Scenario A are summarised in Table 5 below (detailed further in TAR 436).

Table 5: Funding Scenario A base case definition

Treatment	Pharmaceutical price	Clinical effectiveness
1 L monotherapy	Atezolizumab 1200mg 3-weekly	Pembrolizumab OS and PFS (Reck et al., 2021)
1L combination therapy	First 5 months: Pembrolizumab 200mg 3-weekly Months 6+: Pembrolizumab 400mg 6-weekly	Pembrolizumab combination therapy OS and PFS (see TAR 436, table 12)
2L monotherapy	Atezolizumab 1200mg 3-weekly	Average of OS and PFS for atezolizumab, pembrolizumab and nivolumab 2L trials (see TAR 436, table 13)

1L monotherapy

At the time of analysis, the most cost-effective agent with a positive recommendation was S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j). Clinical effectiveness was based on S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j).

1L combination therapy

Pembrolizumab was the only agent that had received a positive recommendation for combination therapy at the time of analysis.

2L monotherapy

All three agents had received a positive recommendation. The most cost-effective of these agents was, at the time of analysis, S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j). Clinical effectiveness was based on an

average of OS and PFS probabilities for all three agents based on clinical advice that it would be reasonable to assume a class effect for ICIs in 2L monotherapy (CTAC April 2022). In the second-line setting, all three trials were considered to be adequately powered.

The incremental cost of ICI funding Scenario A is estimated to be S 9(2)(b) with a QALY gain of 0.95. The incremental cost effectiveness ratio (ICER) is therefore S 9(2)(b) and the estimated QALYs per $1million is S 9 (2)(b) These results are presented in Table 6 below.

Table 6: Cost-effectiveness summary – Funding Scenario A

Item	Value
Incremental QALYs gained	0.95
Incremental costs	S 9(2)(b)
ICER	S 9(2)(b)
QALYs gained per $m	S 9

These results represent a slight decrease in cost-effectiveness when compared to proposal E in TAR 436 (results on page 53). the most comparable proposal in the previous analysis. This change is primarily due to the inclusion of hospitalisation costs for all lung cancer patients, which adds more cost to the intervention arm of the model since patients tend to live longer on ICI treatment, and therefore incur more hospitalisation costs.

Sensitivity analysis is presented in Table 7 below.

Table 7: Sensitivity results – Funding Scenario A

Sensitivity scenario	Base case value	Sensitivity value	QALYs per $m
First-line model			
Base case	-	-	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
Probability of death in the comparator arm uses the chemotherapy lower CI HR of 0.34 from the 2019 KEYNOTE 024 trial (Reck et al., J Clin Onc, 2019: 37:537-546.)-	0.058 NSQ; 0.056 SQ	0.08053	
Probability of death in the comparator arm of the model based on the 2019 KEYNOTE 024 trial - chemotherapy ITT HR of 0.63 (Reck et al., 2019.)-	0.058 NSQ; 0.056 SQ	0.046032	
Cost of monitoring included in BSC + progressed disease health state both arms	$1,131	$1,131	
Cost of disease monitoring * 1.5	$1,131	$1697	
Difference in utility between PFS and PD health states halved (applied to PFS)	0.70	0.64	
Comparator arm - proportion receiving docetaxel	50%	0%	
Comparator arm - proportion receiving docetaxel	50%	100%	

Sensitivity scenario	Base case value	Sensitivity value	QALYs per $m
First-line model			
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
CUA lower bound			
CUA higher bound			
Second-line model			
Base case			
Incremental difference in probability of OS reduced by 25% - applied to intervention arm	ICI 0.054, Doce 0.078	0.06	
Incremental difference in probability of OS increased by 25% - applied to intervention arm	ICI 0.054, Doce 0.078	0.048	
Cost of monitoring included in BSC + progressed disease health state both arms	$1,131	$1,131	
Cost of disease monitoring * 1.5	$1,131	$1,696.5	
Difference in utility between PFS and PD halved (applied to PFS)	0.70	0.64	
Comparator arm - proportion receiving doctaxel	50%	0%	
Comparator arm - proportion receiving doctaxel	50%	100%	
Atezolizumab OS and PFS data from the OAK trial (Rittmeyer et al., The Lancet, 2017: 389:255-65) used (instead of class average)	OS: 0.054, PFS: 0.115	OS: 0.050, PFS: 0.172	
Nivolumab OS and PFS data from CheckMate 017 (Brahmer et al., NEJM, 2015; 373:123-35) and CheckMate 057 (Borghaei et al., NEJM: 2015; 373: 1627-39) used (instead of class average)	OS: 0.054, PFS: 0.115	OS: 0.057, PFS: 0.117	
Pembrolizumab OS and PFS data from KEYNOTE-010 (Herbst et al., The Lancet, 2016; 387:1540-50) used (instead of class average)	OS: 0.054, PFS: 0.115	OS: 0.055, PFS 0.056	
CUA lower bound			
CUA higher bound			

The analysis shows that the CUA results, particularly those of the 1L model, are relatively insensitive to most input parameters due to the high pharmaceutical cost of each ICI.

The 1L model is most sensitive to the probability of death in the comparator arm and S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

- The lower end of the CUA range is informed by the use of S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
- The higher end of the CUA range is informed by applying the lower bound of the hazard ratio (HR) of death in the crossover-adjusted chemotherapy-arm from the KEYNOTE-024 2019 analysis, which results in a probability of death of 0.08053.

The 2L model is most sensitive to the OS estimates, the proportion of patients receiving docetaxel treatment, and the use of single agent efficacy parameters instead of an average across the three agents.

- The lower end of the CUA range is informed by the use of pembrolizumab OS and PFS curves from KEYNOTE-010
- The higher end of the CUA range is informed by the use of atezolizumab OS and PFS curves from the OAK trial.

These results show that the assumption of a 'class effect' i.e., that each ICI agent provides the same or similar therapeutic benefit is the key driver of cost-effectiveness of any single agent.

To estimate the overall likely CUA range for Funding Scenario A, a weighted average of the CUA ranges for the 1L and 2L models is required. To estimate this weighting, the CUA upper- and lower-bounds were weighted by the proportion of total patients who received each line of treatment. Each weighting was calculated as the present value (using an annual discount rate of 3.5%) of patients receiving each line of treatment over the first ten-years of listing, divided by the total number of patients receiving treatment.

The calculation of these weightings is presented in Table 8 below. The approach to estimating patient numbers is detailed in section 4.

Table 8: Bundle weighting used for Funding Scenario A

Item	Year of listing										Weighting	
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10	PV (3.5% disc.)	Weights
Estimated patient numbers on 1L treatment	413	523	634	628	634	641	647	654	660	667	**5,200**	**93.3%**
Estimated patient numbers on 2L treatment	318	40	20	0	0	0	0	0	0	0	**375**	**6.7%**

Finally, the likely CUA range of Funding Scenario A was estimated by multiplying the lower bound of both models by the corresponding weight i.e.

$$Scenario\ A\ Lower\ bound$$
$$= 1L\ model\ lower\ bound * 1L\ weight + 2L\ model\ lower\ bound * 2L\ weight$$
$$= \text{S 9(2)(b)(ii)} * 93.3\% + \text{S 9(2)(b)(ii)} * 6.7\% = \text{S 9(2)(b)(ii)}$$

The same process was repeated for the higher bound, giving a **likely CUA range of** S 9(2)(b)(ii) **QALYs per $m** for Funding Scenario A.

Funding Scenario B: 2L monotherapy (all-comers)

The base case parameter specification for funding Scenario B (detailed further in TAR 436) is summarised in Table 9 below.

Table 9: Funding Scenario B base case definition

Treatment	Pharmaceutical price	Clinical effectiveness
2L monotherapy	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	Average of OS and PFS for atezolizumab, pembrolizumab and nivolumab 2L trials (see TAR 436, table 13)

The incremental cost of Funding Scenario B is estimated to be $29,431, with a QALY gain of 0.42. The ICER is therefore S 9(2)(b)(ii), 9(2)(ba)(i) & and the estimated QALYs per $1million is S 9(2)(b)(ii) These results are presented in Table 10 below.

Table 10: Cost-effectiveness summary – Funding Scenario B

Item	Value
Incremental QALYs gained	0.42
Incremental costs	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
ICER	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
QALYs gained per $m	S 9(2)(b)(ii)

These results represent a significant decrease in cost-effectiveness when compared to proposal B in TAR 436 (results on pages 49-50), the most comparable proposal in the previous analysis. This change is primarily due to the inclusion of hospitalisation costs for all lung cancer patients, which adds more cost to the intervention arm of the model since patients tend to live longer on ICI treatment, and therefore incur more hospitalisation costs.

The sensitivity analysis is the same as the 2L sensitivity analysis presented in Table 7 above.

The likely CUA range of Funding Scenario B **is** S 9(2)(b)(ii), 9 **QALYs per $m.**

3.2 Summary of Cost-Effectiveness

As outlined above, the base-case QALY per $1m estimate is S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) . Taking into account uncertainty in OS and PFS estimates, the updated cost-effectiveness range is S 9(2)(b)(ii), 9 QALYs per $m for Funding Scenario A, and S 9(2)(b)(ii), 9(2) QALYs per $m for Funding Scenario B. There is more uncertainty around the cost-effectiveness for Funding Scenario B since the difference in OS and PFS between agents is greater in a 2L setting.

4 Budget Impact Analysis

The budget-impact analysis undertaken to estimate the cost of funding ICIs for NSCLC is the same as in TAR 436, with the following amendments:

- Overall model changes to reflect updated funding scenarios (described in section 1.1)
- Adjustments to eligible patient numbers
- Adjustments to the number of patients on treatment based on the current proportion on systemic therapy and likely uptake following the listing of an ICI.

The results presented in this section are superseded by those in the RFP section. The RFP results reflect updated prices and additional clinical advice.

Updated eligible patient numbers

In the CTAC April 2022 meeting, the Committee reviewed the assumptions used to arrive at an estimate of eligible patient numbers for 1L treatment. These original assumptions are detailed in Table 30 in TAR 436. The assumptions that have been adjusted or added in this update are detailed below.

- The Committee noted a New Zealand-based study (Aye et al. Cancer Epidemiol. 2020;69:101847) that reported rates of EGFR mutations to be approximately 20%. Pharmac staff therefore used the 20% rate of EGFR mutations instead of the previous rate of 31.6%.
- Of the 248 patients who are diagnosed with non-metastatic disease (stage 1-2), 186 are estimated to have neither the EGFR nor the ALK mutation, and 42% are expected to have recurrent disease following surgical resection (Sugimura et al., Ann Thor Surg, 2007; 83:2), which indicates that an additional 78 (186 * 42%) patients would be treated per year.
- The Committee considered that "there would be an additional cohort of ICI eligible patients within the first 2-3 years of funding comprised of stage III NSCLC patients whose disease has metastasized post chemotherapy, and who did not receive durvalumab treatment. The Committee considered that this may add an additional 60 patients to the ICI eligible cohort"

The updated estimated number of eligible 1L patients is presented in Table 11 below.

Table 11: Estimated eligible patient numbers

Assumption	Estimate	Source/rationale
Number of people diagnosed with NSCLC, 2015-18	6,023	Lung Cancer Quality improvement report. Te Aho Te Kahu, 2021. p8
People with newly diagnosed NSCLC per year	1,506	6,023 / 4 (2015-18 encompasses 4 years)

Assumption	Estimate	Source/rationale
Proportion of patients with metastatic disease at diagnosis	83.50%	Lawrenson et al., NZMJ 2018; 131:1479
Patients with NSCLC with metastatic disease	1,257	1,506 * 83.5%
Proportion with EGFR mutation	20%	Aye et al., 2020
Proportion with ALK+ mutation	5%	Chia et al., Clin Epidemiol. 2014; 6: 423-432
Number of patients with no EGFR or ALK mutation	943	1,257 * (1 - 20% - 5%)
Patients diagnosed with Stage 1-2 disease (as above - new patients less people with metastatic disease)	248	1,506 – 1,257
Number of patients with no mutation	186	248 * (1 – 20% - 5%)
Proportion progressing to stage 3-4	42%	Sugimura et al., 2007 (445 / 1,073 had disease recurrence)
Number progressing to Stage 3-4	78	186 * 42%
People with stage 3 disease who relapsed and did not receive Durvalumab (per year, over first 3 years of listing)	20	60 patients divided over 3 years
Total eligible patients in first year of listing	**1,041**	**943 + 78 +20**

Updated estimated patients on treatment

Previously, uptake of ICIs was assumed to be 100%, based on the high health need of patients with metastatic NSCLC and improved efficacy compared to current treatments. However, evidence from Te Aho o te Kahu (Cancer Control Agency) suggests that current use of systemic anti-cancer therapy among people with NSCLC is significantly lower, at 29.7% (table 7, Te Aho, 2021).

It was considered likely that this rate would increase over time with the funding of an ICI treatment, but that it was still not appropriate to assume that all patients would pursue systemic therapy. Therefore, an additional 10% cumulative uptake for each of the first three years of listing was assumed i.e., uptake is 39.7% in year 1, 49.7% in year 2, and 59.7% thereafter. This assumption is in line with CTAC advice, however, it is noted that there is limited evidence to inform uptake.

Budget Impact of Funding Scenario A

The budget impact of Funding Scenario A is presented in Table 12 below. The pharmaceutical cost is based on the pharmaceutical prices as detailed in Table 5, while the health sector cost is based on the TreeAge model costs for the first five years. It is assumed that PDL-1 testing would become reflex (i.e., would occur in almost all cases) by the third year of listing in the 1L setting.

Table 12: Budget impact of Funding Scenario A

	Year 1	Year 2	Year 3	Year 4	Year 5	NPV (8% discount rate)
First-line						
Eligible patients	1,041	1,052	1,062	1,052	1,063	-
Uptake	39.7%	49.7%	59.7%	59.7%	59.7%	-
Estimated patients initiating treatment	413	523	634	628	634	-
Proportion PDL-1 tested	32%	66%	100%	100%	100%	-
Pharmaceutical costs ($m)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Other health sector costs ($m)	$0.82	$3.03	$5.65	$8.06	$10.11	**$22.30**
Total health sector budget impact ($m)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Second-line						
Eligible patients	800	397	197	98	48	
Uptake	39.7%	49.7%	59.7%	59.7%	59.7%	
Estimated patients initiating treatment	318	40	20	0	0	
Proportion PDL-1 tested	0%	0%	0%	0%	0%	
Pharmaceutical costs ($m)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Other health sector costs ($m)	$1.18	$1.10	$0.71	$0.40	$0.21	**$3.27**
Total health sector budget impact ($m)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Overall Impact of proposal ($m)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

Budget Impact of Funding Scenario B

The budget impact of Funding Scenario B is presented in Table 13**Table *13*** below. The pharmaceutical cost is based the pharmaceutical prices as detailed in Table 9, while the health sector cost is based on the TreeAge model costs for the first five years. There is no PDL-1 testing since PDL-1 expression > 50% is not a requirement to receive ICI treatment in the 2L setting.

Table 13: Budget impact of Funding Scenario B

	Year 1	Year 2	Year 3	Year 4	Year 5	NPV (8% discount rate)
Second-line						
Prevalent patients	318	40	20	0	0	
Incident patients	211	300	372	380	384	
Estimated patients initiating treatment	528	340	391	380	384	

Proportion PDL-1 tested	0%	0%	0%	0%	0%	
Pharmaceutical costs	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Other health sector costs	$1.96	$2.84	$3.33	$3.59	$3.73	**$13.03**
Total health sector budget impact	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

5 RFP Analysis

RFP Information

On 6 July 2022, Pharmac released a request for proposal (RFP) for the supply of ICIs for the treatment of NSCLC. For more information, please see the RFP document (Pharmac website link – objective ID is A1593389). [redacted]

[redacted]

The net price per vial offered in [redacted] is displayed in Table 14 on the following page. [redacted]

Table 14: Per unit pricing

All Pricing Received	1L Monotherapy		1L Combination Therapy		2L Monotherapy		
	List Price	Net Price	List Price	Net Price	List Price	Net Price	Notes
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	[redacted]						
					Scenario B bid, 2L monotherapy Onlv bids		
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	[redacted]						

Modelling updates

After bids were received, CUA and BIA results were updated to reflect:

- S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
S 9(2)(b)(ii), 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
- Resolution of a modelling error that caused chemotherapy costs (pemetrexed), particularly in the comparator arm of the model, to be overestimated
- Additional clinical advice sought, S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

These changes are described in detail below.

Chemotherapy cost update

In the process of updating the model to reflect S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) the RFP, an error in the model was found that caused weekly pemetrexed costs to be overstated. This error caused chemotherapy costs to be overestimated, particularly in the comparator arm. The costs of pemetrexed are now implemented correctly.

Additional clinical advice

On 14 October 2022, an ad-hoc CTAC meeting was held to inform the clinical and economic evaluation of bids for the RFP. All agents in each indication received a positive funding recommendation given the high health need of people with NSCLC and the likely benefit of funding any treatment if even only one was affordable, given the available budget. Modelling-related CTAC advice and the corresponding updates made are presented in Table 15 below. For a full description of the advice received, which also relates to other elements of the RFP beyond the CUA and BIA, please see the following records:

- 1L monotherapy (record not published at the time of writing, all published CTAC records can be found here). S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
- 1L combination therapy (record not yet published). Agents considered were S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
S 9(2)(b)(ii), 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j).
- 2L monotherapy (record not yet published). S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

Table 15: CTAC advice and modelling updates for RFP

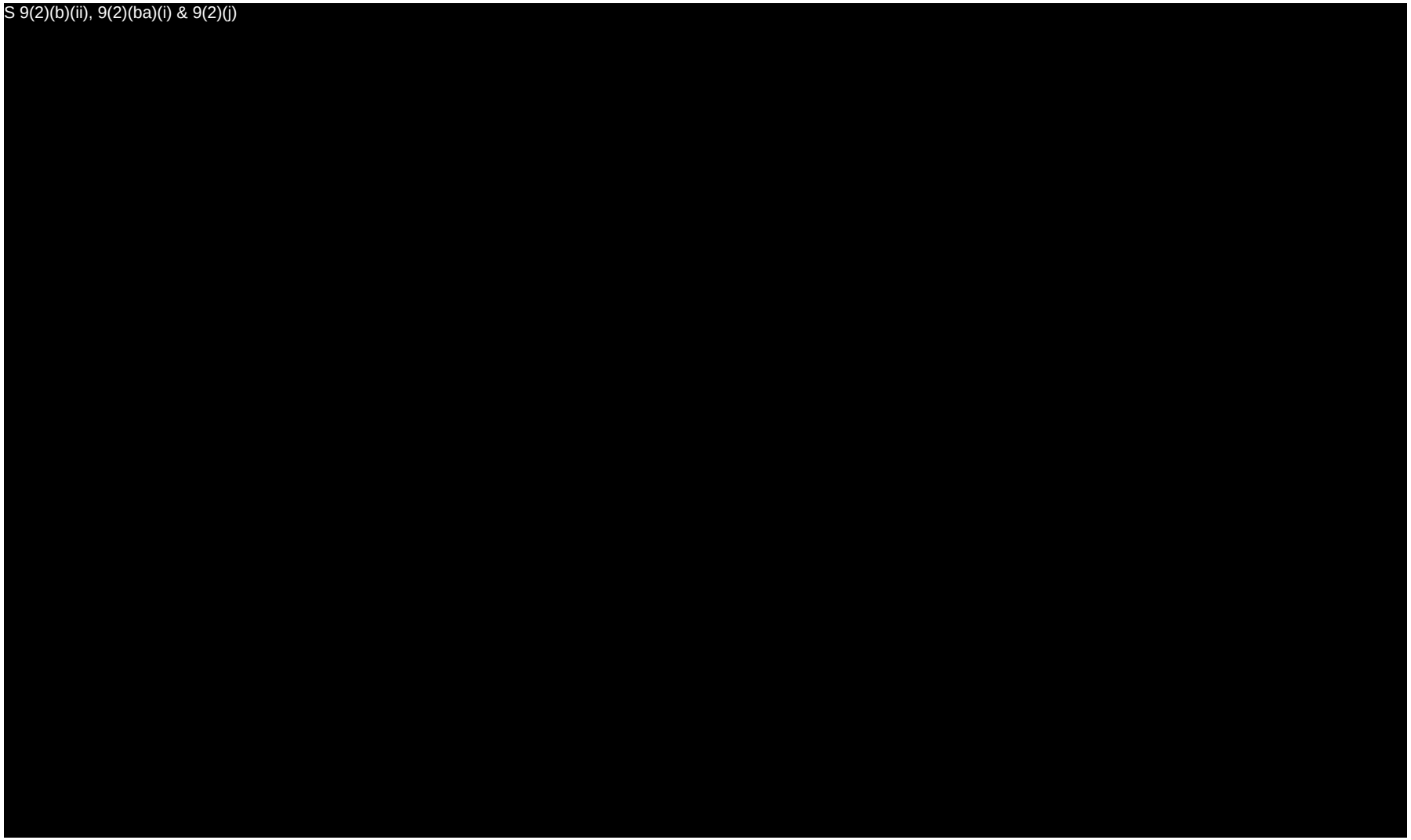
CTAC Discussion	Modelling update(s)
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	

CTAC Discussion	Modelling update(s)
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
An ICI should be available for the ~10% of people may not be able to undergo a biopsy to test for EGFR/ALK mutations, which may mean more patients receive treatment than currently estimated	Patient numbers were updated to include people with EGFR/ALK mutation statuses aligned with the special authority criteria for 90% of the population, and to include all of the remaining 10% assumed ineligible for a biopsy. Treatment efficacy was not adjusted since only a very small proportion of people would have these mutations, and it is not clear that people with either mutation would receive no clinical benefit/
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	

CTAC Discussion	Modelling update(s)
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) [redacted]	[redacted]
The choice of chemotherapy regimen for use to model the counterfactual and the combination therapy used with an ICI, would be based on the person's histology and would not differ across agents. S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) [redacted] S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) [redacted] S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) [redacted]	Model updated to reflect relevant chemotherapy regimens. For completeness, the chemotherapy regimens are described in Table 16 below.
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) [redacted]	[redacted]
The proportion of people who receive docetaxel in subsequent treatment lines was expected to be lower than currently modelled (50%).	The proportion of people who receive docetaxel in as 2L or 3L treatment was changed to 30%. It was considered reasonable to use the same proportion for 2L and 3L since it was not clear if people would be more likely to receive docetaxel after chemotherapy only or after chemotherapy and an ICI.

Table 16: Chemotherapy regimens provided in combination therapy with each agent

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



Page 33 withheld in full under S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

Savings on currently listed pharmaceuticals

The terms of the RFP allowed respondents to offer price reductions on pharmaceuticals already funded by Pharmac as part of their bid. S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

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

CUA and BIA Results

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

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

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

Table 17: S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

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

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

Table 18: S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

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

Table 19: S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)

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

Page 37 withheld in full under S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)