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

Last updated: November 2021

This technology assessment report (TAR) summaries the key considerations, inputs, assumptions and areas of uncertainty in the cost-effectiveness and budget impact assessment of immune checkpoint inhibitors (ICI inhibitors) for metastatic non-small cell lunger caner (NSCLC). This TAR supersedes previous Technology Assessment Reports for ICI inhibitors for metastatic NSCLC and summates Pharmac's considerations of ICI inhibitors for metastatic NSCLC in first line and second line settings to date.

A summary of the Immune Checkpoint inhibitors considered is provided in the three subsequent tables below.

PROPOSAL OVERVIEW	
Pharmaceutical	Atezolizumab (Tecentriq)
Supplier	Roche
Proposed Indication	• 1L monotherapy PD-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: $9503 gross, S 9(2)(b) net, S 9(2) net per mg. Commercial offer received June 2020 (A1361252)
PTAC PRIORITY	1L monotherapy PD-1 expression >50% • High – CaTSoP July 2020 1L combination therapy • Decline - CaTSoP April 2019 due to insufficient evidence for this combination. • Decline – CaTSoP July 2019 2L monotherapy • PTAC considered in Feb 2016. • LOW - PTAC Aug 2017 • LOW - CaTSoP Aug 2017
Pharmconnect	• 1L monotherapy • 1L combination therapy • 2L monotherapy Related bundle proposals • Bundle - PD-1 inhibitors - Metastatic NSCLC lung cancer (1L and 2L) • Bundle - PD-1 inhibitors - Metastatic NSCLC lung cancer (1L monotherapy and 1L combination therapy) • Bundle - PD-1 inhibitors - Metastatic NSCLC lung cancer (1L PD-1 high, 2L PD-1 low)

PROPOSAL OVERVIEW	
Pharmaceutical	Nivolumab (OPDIVO)
Supplier	Bristol-Myers Squibb
Proposed Indication	2L monotherapy
Dosing	• 240mg, 2-weekly • 480mg, 4-weekly
Pharmaceutical Price	40mg vial: $1051.98 gross, S 9(2) net, S 9(2) net per mg 100mg vial: $2629.96 gross, S 9(2)(b) net, S 9(2) net per mg Pharmac contract 2016 (A901169)
PTAC Priority	2L monotherapy • PTAC considered in Feb 2016; no formal recommendation. • LOW-MED - CaTSoP April 2016 • LOW - PTAC May 2016
PHARMConnect	• 2L monotherapy • 2L – monotherapy squamous Related bundle proposals • Bundle - PD-1 inhibitors - Metastatic NSCLC lung cancer (1L and 2L) • Bundle - PD-1 inhibitors - Metastatic NSCLC lung cancer (1L monotherapy and 1L combination therapy) • Bundle - PD-1 inhibitors - Metastatic NSCLC lung cancer (1L PD-1 high, 2L PD-1 low)

PROPOSAL OVERVIEW	
Pharmaceutical	Pembrolizumab (Keytruda)
Supplier	Merck Sharp & Dohme
Proposed Indication	• 1L monotherapy PD-1 expression>50% • 1L combination therapy: • 2L monotherapy
Dosing	• 200mg, 3-weekly, • 400mg, 6-weekly
Pharmaceutical Price	100mg vial: $4680 gross, S 9(2)(b) net, S 9(2) 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 – CaTSoP Nov 2018 • MED – PTAC Feb 2019 • HIGH – CaTSoP Apr 2019 1L combination therapy • MED – PTAC Nov 2018 • MED – PTAC Feb 2019 2L monotherapy • LOW - PTAC Nov 2016 • LOW – CaTSoP Mar 2017 • LOW – PTAC Aug 2017
PHARMConnect	• 1L monotherapy • 1L combination therapy • 2L monotherapy Related bundle proposals • Bundle - PD-1 inhibitors - Metastatic NSCLC lung cancer (1L and 2L) • Bundle - PD-1 inhibitors - Metastatic NSCLC lung cancer (1L monotherapy and 1L combination therapy) • Bundle - PD-1 inhibitors - Metastatic NSCLC lung cancer (1L PD-1 high, 2L PD-1 low)

Executive Summary

Pharmac has received several funding applications for Immune Checkpoint Inhibitors for the first line or second line treatment of metastatic non-small cell lung cancer (NSCLC). At the time of writing this TAR, Pharmac had a positive clinical advice recommendation to fund either atezolizumab, pembrolizumab or nivolumab for second line treatment, atezolizumab or pembrolizumab for first line monotherapy therapy and pembrolizumab for first line combination therapy.

Lung cancer was the fifth most common cancer registered in New Zealand in 2013, accounting for 9.2% percent of all registrations and it was the leading cause of cancer death, accounting for 1/5 of deaths from cancer and almost a third of all Māori cancer deaths. The Ministry of Health Cancer Patient Survival, 1994-2011, report notes that the 5 and 10-year cumulative relative survival for lung cancer patients is 11.5% and 9.8%, respectively.

Patients with metastatic lung cancer currently receive a platinum-based chemotherapy regimen as first-line therapy (carboplatin or cisplatin in combination with pemetrexed (non-squamous histology only) or paclitaxel, gemcitabine (squamous histology only)). Second-line treatment is with docetaxel, though not all patients will receive this due to toxicity.

Summary of Pharmac Cost-Utility Analysis and Budget Impact Analysis

Clinical advice received suggested there was several different funding scenarios with respect to immune check point inhibitors. These scenarios differed by the line of therapy being funded, whether or not a PD-L1 test would be required and whether or not access criteria specified a PD-L1 threshold to access treatment. Two separate cost-utility models were created, one for first line therapy and one for second line therapy. The cost-effectiveness of immune checkpoint inhibitors was explored (Table 1) using these models. The modelled results will be updated upon receipt of a new commercial proposal.

Table 1: Summary of cost-effectiveness estimates by scenario

Scenario		**Agent modelled**	**Likely Range** (QALYs per $ million spent)	**5-year NPV CPB*** ($ million)	**5-year NPV DHB*** ($ million)
A	ICI for 1L monotherapy – patients with PD-L1 expression >50% only	Atezolizumab 1200mg 3 weekly	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)		$4.89
B	ICI funded for second line use only	Atezolizumab 1200mg 3 weekly			$9.38
C	ICI funded for first line use (monotherapy and combination therapy)	Atezolizumab 1200mg 3 weekly monotherapy, Pembrolizumab 400mg , 6 weekly combination			$8.42 (with PD-1 test) $5.45 (no PD-L1 test)
D	ICI funded for first line use in patients with PD-1 >50% and second line in patients with PD-1>50%	Atezolizumab 1200mg 3 weekly			$11.27
E	ICI funded for use first line and second line – one line permitted per patient	Atezolizumab 1200mg 3 weekly monotherapy, Pembrolizumab 400mg , 6 weekly combination			$10.73

*8% annual discount rate for BIA, 3.5% for CUA as per PFPA
Comparator first line: platinum-based chemotherapy followed by docetaxel
Comparator second line: docetaxel
Note: first line monotherapy is adding a line of therapy, first line combination therapy is adding an ICI on to current first line treatment

1. Proposal Overview

1.1 Summary

Pharmac has received several applications for the funding of immune checkpoint inhibitors (ICIs) for first line or second use in patients with metastatic, Epidermal Growth Factor Receptor (EGFR) and Anaplastic Lymphoma Kinase Positive (ALK+) wildtype, non-small cell lung cancer (NSCLC). The individual agents, the ICI class and each line of therapy has been reviewed by PTAC and CaTSoP on several occasions. This TAR outlines the health technology assessment undertaken for several proposals (listed below) and supersedes all previous Pharmac assessment of ICI in the metastatic NSCLC setting.

Proposals considered in this TAR are for patients with EGFR and ALK wildtype, metastatic NSCLC:

1) An immune checkpoint inhibitor as a first line monotherapy for patients with a PD-1 expression of >50% (PHARMConnect link: Atezolizumab, Pembrolizumab)
2) An immune checkpoint inhibitor in combination with chemotherapy for first line use (PHARMConnect link: Pembrolizumab)
3) An immune checkpoint inhibitor for second line use, PD-1 all comers (PHARMConnect link: Atezolizumab, Nivolumab, Pembrolizumab)
4) Bundle of A and B (PHARMConnect link)
5) Bundle of A plus a proposal for second line use for patients with a PD-1 expression less than 50% (patients who would not have accessed a PD-1 inhibitor in a 1L setting, including those who have already commenced first line treatment. (PHARMconnect link)
6) Bundle of A, B and C (PHARMconnect link)

Three separate PICO statements (patient population; intervention; comparator treatment; and main outcomes of treatment) covering the three primary distinct groups (A, B and C) considered in this assessment are outlined below. The PICO's are further explained in the treatment paradigm in Figure 2.

Table 2: PICO statement for 1L EFGR and ALK wild-type patients with a PD-1 expression of greater than 50% - monotherapy

PICO	
Population	Patients with EGFR-wildtype, metastatic non-small cell lung cancer who have not yet received any treatment for their metastatic disease and have a PD-1 expression higher than 50%.
Intervention	1L: ICI 2L: Platinum based chemotherapy 3L: Docetaxel
Comparator	1L: Platinum based chemotherapy 2L: Docetaxel
Outcome	Improvement in the time to disease progression (improvement in progression free survival (PFS)) and time to death (improvement in overall survival (OS))

Table 3: PICO statement for 1L EFGR and ALK wild-type patients in combination with chemotherapy

PICO	
Population	Patients with EGFR-wildtype, metastatic non-small cell lung cancer who have not yet received any treatment for their metastatic disease.
Intervention	1L: ICI in combination with chemotherapy 2L: Docetaxel
Comparator	1L: Platinum based chemotherapy 2L: Docetaxel
Outcome	Improvement in the time to disease progression (improvement in progression free survival (PFS)) and time to death (improvement in overall survival (OS))

Table 4: PICO statement for 2L EGFR and ALK wild-type patients (monotherapy)

PICO	
Population	Patients with EGFR-wildtype, metastatic non-small cell lung cancer who have progressed following first line treatment for their metastatic disease.
Intervention	2L: ICI 3L: Docetaxel
Comparator	2L: Docetaxel
Outcome	Improvement in the time to disease progression (improvement in progression free survival (PFS)) and time to death (improvement in overall survival (OS))

1.2 Patient Population

Lung cancer in general

Lung cancer was the fifth most common cancer registered in New Zealand in 2016 with 2,229 registrations comprised of 445 Māori cases and 1784 non-Māori cases with similar incidence between the sexes. Of the 2016 lung cancer registrations, 1,623 (72.8%) were 65+ years of age. Lung cancer registration rates for Māori in 2016 were 75.5 per 100,000 for males and 79.4 per 100,000 for females; rates for non-Māori males and females in the same year were 26.7 and 22.1 per 100,000, respectively.

Between 2014 and 2016, the number of lung cancer registrations was relatively stable with an overall compound annual growth rate of -0.4%. The compound annual growth rate for new registrations was highest for Māori males (1.0%) and for non-Māori females (0.9%), and lowest for non-Māori males (-1.9%).

Lung cancers were the leading cause of cancer death in 2016, accounting for ~1/5 cancer deaths and ~1/3 of all Māori cancer deaths. In 2016, there were 1825 deaths due to lung cancer in New Zealand with an overall compound annual growth rate of 1.9% compared to 2014. The highest compound annual growth rates for lung cancer deaths between 2014 and 2016 were for Māori males (3.1%), non-Māori males (2.4%) and Māori females (2.2%).

Source – Atezolizumab in combination with bevacizumab and platinium-based chemotherapy, CaTSoP paper April 2019.

Types of lung cancer

There are two main types of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC accounts for approximately 80% of all lung cancers and can be further categorized into two subtypes: squamous cell carcinomas and non-squamous carcinomas (including adenocarcinoma and large cell histologies). Molecular diagnostics are used to further categorise patients by targetable oncogenic alterations (i.e. EGFR, ALK, ROS1, or BRAF) or by immunotherapy markers (i.e. PD-L1).

The proposals being assessed in this TAR are for NSCLC patients with trial evidence often split or stratified to represent specified sub-populations based on PD-1 tumour expression or tumour histology (squamous or non-squamous histology). The later, tumour histology is material due to the different treatment paradigms associated with each (outlined in section 1.3 below).

Metastatic lung cancer

Lung cancer is often diagnosed when the disease is at the metastatic stage. In New Zealand, approximately 62% of lung cancers are metastatic at diagnosis. (Lawrenson et al, 2018). The survival rate of metastatic lung cancer is also low with an estimated 5-year relative survival rate of 6% reported by the American Cancer Society for those with distant disease compared to 61% if the disease is localised.

There are several oncogenic targets that have been identified with lung cancers which can be tested, and treatments can be targeted. The proposal being assessed in the TAR does not include those

patients with an identified oncogenic target for which a funded target treatment is available. In New Zealand, this is the presence of an EGFR or ALK mutation.

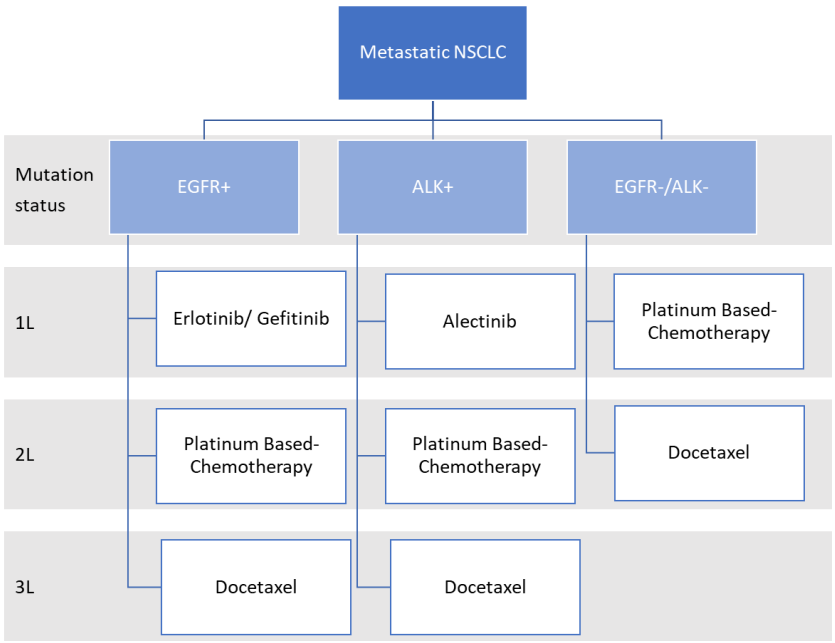
1.3 Current Treatment in New Zealand

Metastatic NSCLC

The current treatment paradigm for metastatic NSCLC in New Zealand is outlined in Figure 1 below.

First line treatment consists of gefitinib and erlotinib for those patients who have had an EGFR mutation identified and alectinib for those patients who have had an ALK mutation identified. Second line treatment for patients who have progressed on first line targeted therapies or first line treatment for patients who do not have an identified mutation is platinum-based chemotherapy. The platinum component can be either carboplatin or cisplatin with the choice of agent largely driven by their differing toxicity and administration profiles. The chemotherapy agent in New Zealand is primarily paclitaxel for patients with squamous histology and pemetrexed for patients with non-squamous histology. Following progression on platinum-based chemotherapy, a proportion of patients will receive docetaxel. Due to the high side-effect profile of this treatment, treatment is more likely in patients deemed fit to receive it.

Figure 1: Current NSCLC treatment paradigm - New Zealand



1.4 Intervention

Atezolizumab
Atezolizumab is an intravenous infusion administered at a dose of 840mg every 2 weeks, 1200mg every 3 weeks or 1680 mg every 4 weeks. The first dose is recommended to occur over a 60min period, with subsequent treatment if tolerated being administered over 30mins. It is recommended that treatment with atezolizumab be continued until disease progression, unacceptable toxicity or death. Atezolizumab is Medsafe registered for a number of indications including the following relevant lung cancer indications:

- in combination with bevacizumab, paclitaxel and carboplatin, for the first-line treatment of patients with metastatic non-squamous non-small cell lung cancer (NSCLC).
    - In patients with EGFR mutant or ALK-positive NSCLC, Tecentriq, in combination with bevacizumab, paclitaxel and carboplatin, is indicated only after failure of appropriate targeted therapies.

- in combination with paclitaxel and carboplatin, for the first-line treatment of patients with metastatic non-squamous NSCLC who do not have tumour EGFR or ALK genomic aberrations and whose tumours have PD-L1 expression ≥ 1%
- as monotherapy for the first-line treatment of adults with metastatic NSCLC whose tumours have high PD-L1 expression (PD-L1 stained ≥ 50% of tumour cells [TC ≥ 50%] or PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥ 10% of the tumour area [IC ≥ 10%]) as determined by a validated test, and who do not have EGFR or ALK genomic tumour aberrations.
- as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC after prior chemotherapy

Nivolumab

Nivolumab is an intravenous infusion administered at a dose 3mg/kg every 2 weeks, 240mg every 2 weeks or 250mg every 4-weeks. It is recommended that the infusion be administered over 30mins. It is recommended that treatment with nivolumab be continued until disease progression, unacceptable toxicity or death. Nivolumab is Medsafe registered for a number of indications including the following lung cancer indications:

- as monotherapy for the treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy.
- as monotherapy for the treatment of locally advanced or metastatic non squamous non-small cell lung cancer (NSCLC) with progression on or after prior chemotherapy. In patients with tumour EGFR or ALK genomic aberrations, Nivolumab should be used after progression on or after targeted therapy.

Pembrolizumab

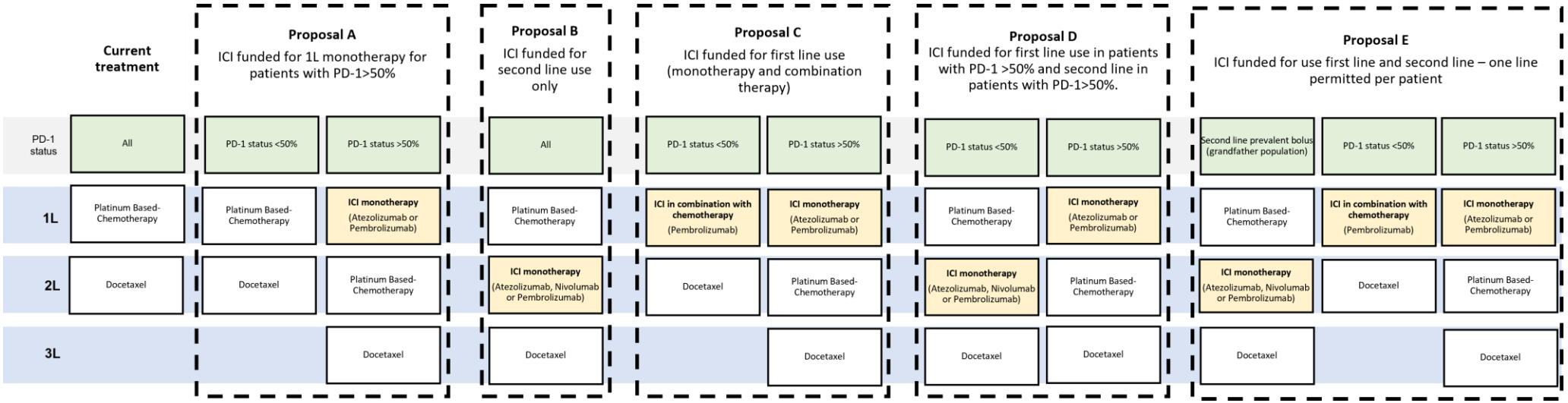
Pembrolizumab is an intravenous infusion administered at a dose 200mg every 3 weeks or 400mg every 6 weeks (note: 2mg/kg is also indicated for previously treated NSCLC). It is recommended that the infusion be administered over 30mins. It is recommended that treatment with pembrolizumab be continued until disease progression, unacceptable toxicity or death. Pembrolizumab is Medsafe registered for a number of indications including the following lung cancer indications:

- in combination with pemetrexed and platinum chemotherapy, for the first-line treatment of patients with metastatic non-squamous non-small cell lung carcinoma (NSCLC), with no EGFR or ALK genomic tumour aberrations.
- in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of patients with metastatic squamous NSCLC.
- as monotherapy is indicated for the first-line treatment of patients with NSCLC expressing PD-L1 [tumour proportion score (TPS) ≥1%] as determined by a validated test, with no EGFR or ALK genomic tumour aberrations, and is metastatic.
- as monotherapy for the treatment of patients with advanced NSCLC whose tumours express PD-L1 with a ≥1% TPS as determined by a validated test and who have received platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have received prior therapy for these aberrations prior to receiving pembrolizumab

1.5 Proposed treatment paradigm

Figure 2 below details the proposed treatment paradigm for all the proposals being considered in this TAR.

Figure 2: Current and proposed treatment paradigm for all proposals under consideration



Note: Proposals outlined in further detail in section 1.1 above. Green boxes indicate the popualtion being treated by PD-1 status and the yellow boxes indicate the placement of ICI in the relevant treatment paradigms.

2. Health Benefits

2.1 Clinical Evidence

The pivotal clinical trials for ICI treatments in metastatic NSCLC are summarised in the tables below. Table 5 summaries the key trial evidence for ICI as a first line monotherapy in patients with a PD-1 expression greater than 50%.

Table *6* summaries the key trial evidence for first line ICI use in combination with platinum-based chemotherapy. Table 7 summaries the key trial evidence for ICI use in the second line setting for patients regardless of PD-1 expression.

Table 5: Summary of clinical trials evidence for ICI for 1L therapy in combination with chemotherapy for NSCLC patients

Agent	Pembrolizumab	Pembrolizumab
Trial	KEYNOTE 407 Paz-Ares et al, N Engl J Med 2018;379:2040-51.	KEYNOTE189 Gandhi et al, N Engl J Med 2018;378:2078-92
Histology	Squamous	Non-squamous
Therapy Line	First line combination therapy	First line combination therapy
Trial	Phase 3, double blinded RCT	Phase 3, double blinded RCT
Population	559 patients with untreated metastatic stage IV, squamous NSCLC	616 patients with metastatic non-squamous NSCLC (EGFR or ALK wildtype) who had received no previous treatment for metastatic disease.
Intervention	Pembrolizumab (200mg 3-weekly, 35 cycle max) + carboplatin (AUC 6mg, 3-weekly, 4 cycles) + either paclitaxel (200mg/m^2 3-weekly, 4 cycles) or nab- paclitaxel (100mg/m^2 weekly, 12 weeks)	Pembrolizumab (200mg 3-weekly, 35 cycles max) + 4 x 3 week cycles of pemetrexed in combination with a platinum based aged (cisplatin or carboplatin), followed by 3 weekly maintenance pemetrexed (max 35 cycles of total pemetrexed)
Comparison	Placebo + carboplatin (AUC 6mg, 3-weekly, 4 cycles) + either paclitaxel (200mg/m^2 3-weekly, 4 cycles) or nab-paclitaxel (100mg/m^2 weekly, 12 weeks)	Placebo + 4 x 3 week cycles of pemetrexed in combination with a platinum based aged (cisplatin or carboplatin), followed by 3 weekly maintenance pemetrexed (max 35 cycles of total pemetrexed)
Key results	• Median follow-up of 7.8 months • Median OS 15.9 months (95%CI 13.2 to not reached) in the pembrolizumab-combination group and 11.3 months (95% CI, 9.5 to 14.8) in the placebo-combination group • Hazard ratio for death - 0.64; 95% CI, 0.49 to 0.85 • Overall survival benefit was consistent regardless of the level of PD-L1 expression. • The median progression-free survival was 6.4 months (95% CI, 6.2 to 8.3) in the pembrolizumab combination group and 4.8 months (95% CI, 4.3 to 5.7) in the placebo-combination group • Hazard ratio for disease progression or death, 0.56; 95% CI, 0.45 to 0.70	• A median follow-up of 10.5 months • Overall survival at 12 months was 69.2% (95CI, 64.1 to 73.8) in the pembrolizumab-combination group versus 49.4% (95% CI, 42.1 to 56.2) in the placebo-combination group • Hazard ratio for death, 0.49; 95% CI, 0.38 to 0.64 • Median progression-free survival was 8.8 months (95% CI, 7.6 to 9.2) in the pembrolizumab-combination group and 4.9 months (95% CI, 4.7 to 5.5) in the placebo-combination group • Hazard ratio for disease progression or death, 0.52 (95% CI, 0.43 to 0.64)
Adverse events	• Adverse events of grade 3 or higher occurred in 69.8% of the patients in the pembrolizumab-combination group and in 68.2% of the patients in the placebo-combination group. • Discontinuation of treatment because of adverse events was more frequent in the pembrolizumab-combination group than in the placebo-combination group (13.3% vs. 6.4%).	• Adverse events of grade 3 or higher occurred in 67.2% of the patients in the pembrolizumab-combination group and in 65.8% of those in the placebo-combination group.
Notes:	• following centrally confirmed radiologic progression, patients in the control arm were eligible to cross over to receive pembrolizumab monotherapy; and patients could continue open-label pembrolizumab monotherapy despite radiographically confirmed disease progression	• crossover to pembrolizumab monotherapy was permitted among the patients in the control arm who had verified disease progression. .

Note: At the time of analysis Pharmac had not received a positive clinical advice recommendation for the ICI atezolizumab or nivolumab for use in combination with chemotherapy for first line treatment of NSCLC. As a result, the date from these trials is not summarised here or considered in the analysis.

Table 6: Summary of clinical trials evidence for ICI for 1L monotherapy for NSCLC patients

Agent	Pembrolizumab	Atezolizumab
Trial	KEYNOTE-024 Reck et al. NEJM 2016;375:1823-33	IMPOWER110 Conference abstract: Spigel DR, et al. Ann Oncol 2019; 30(Suppl 5):mdz293)
Histology	Squamous and non-squamous	Squamous and non-squamous
Therapy Line	First line	First line
Trial	Open-label, phase 3 RCT	Phase 3 RCT
Population	305 patient, previously untreated advanced NSCLC with PD-1 expression of >50% and no EGFR mutation.	572 patients with previously untreated, stage four NSCLCL with a PD-L1 expression of greater than 1%. (205 patients with PD-L1 expression > 50%).
Intervention	Pembrolizumab 200mg every 3 weeks	Atezolizumab 1200mg every 3 weeks.
Comparison	Platinum-based chemotherapy for 4-6 cycles, until disease progression or adverse event resulting in discontinuation. • carboplatin or cisplatin plus pemetrexed • carboplatin or cisplatin plus gemcitabine, • carboplatin plus paclitaxel Note pemetrexed regimens included maintenance therapy after completion of combination chemotherapy. The most common regimen was carboplatin/pemetrexed	Platinum-based chemotherapy for 4-6 21-day cycles, until disease progression or adverse event resulting in discontinuation. • Non-squamous cisplatin or carboplatin with pemetrexed • Squamous – cisplatin or carboplatin with gemcitabine
Key results	• Median follow-up: 11.2 months (6.3-19.7) • Median PFS: 10.3 months (95% CI, 6.7-NR) in the pembrolizumab arm and 6.0 months (95% CI, 4.2-6.2) in the chemotherapy arm • Hazard ratio for disease progression or death: 0.50 (95%CI 0.37 to 0.68) • Median duration of treatment was 7.0 months or 10.5 cycles in pembrolizumab arm and 3.5 months or 4 cycles in the chemotherapy arm. • The estimated percentage of patients who were alive at 6 months was 80.2% (95% CI, 72.9-85.7) in the pembrolizumab arm and 72.4% (95% CI 64.5-78.9) in the chemotherapy arm. • Median overall survival was not reached in either group. It was reported that OS was significantly longer in the pembrolizumab group than in the chemotherapy group • HR for death: 0.60 (95%CI, 0.41 to 0.89)	• Median follow-up 15.7 months • Median OS in PD-L1 >1% population of 17.5 months with atezolizumab compared to 14.1 months in comparator arm. • OS hazard ratio PD-L1 >1%: 0.832 (95%CI 0.649-1.067) • Median OS in PD-L1 >50% population of 20.2 months with atezolizumab compared to 13.1 months in comparator arm. • OS hazard ratio PD-L1 >50%: 0.595 (95%CI 0.398-0.890) • No PFS data published to date.
Adverse events	• During treatment with the initially assigned therapy, treatment-related adverse events occurred in 73.4% of the patients in the pembrolizumab arm and in 90.0% of the patients in the chemotherapy arm. Grade 3 or greater treatment-related adverse events occurred in 26.6% of patient in the pembrolizumab arm and in 53.3% in the chemotherapy arm. • The most common treatment-related adverse events were diarrhoea (in 14.3% of the patients), fatigue (10.4%), and pyrexia (10.4%) in the pembrolizumab group and anaemia (44.0%), nausea (43.3%), and fatigue (28.7%) in the chemotherapy group.	• Treatment related grade 3-4 adverse events occurred in 12.9% of patients in the atezolizumab arm and 44.1% in the comparator arm.
Notes:	• Crossover from chemotherapy to pembrolizumab was permitted for patients who progressed on chemotherapy. • No treatment guideline post progression on pembrolizumab were provided.	• Intervention arm was treated until disease progression of loss of clinical benefit while the comparator arm was treated until disease progression • Protocol amendments at the end of the trial regarding statistics • Publication in of complete trial in peer-reviewed general pending

Note: At the time of analysis Pharmac had not received an application or a positive clinical advice recommendation for the treatment of the ICI nivolumab for use as a monotherapy for first line treatment of NSCLC. As a result, the date from these trials is not summarised here or considered in the analysis

Table 7: Summary of clinical trials evidence for ICI for 2L monotherapy for NSCLC patients

Agent	Atezolizumab	Nivolumab	Nivolumab	Pembrolizumab
Trial name	OAK Rittmeyer et al, Lancet 2017; 389: 255–65	CheckMate 017 Brahmer et al, N Engl J Med 2015;373:123-35.	CheckMate 057 Borghaei et al, N Engl J Med 2015;373:1627-39.	KEYNOTE-010 Herbst et al, Lancet 2016; 387: 1540–50
Histology	Squamous and non-squamous	Squamous	Non-squamous	Squamous and non-squamous
Trial design	Open-label phase 3 RCT No cross over to atezolizumab was permitted Data stratified by TC expression	Open-label phase 3 RCT	Open-label phase 3 RCT	Open-label phase 2/3 RCT No cross over to atezolizumab was permitted Data stratified by any PD-L1 expression and greater than 50% PD-L1 expression.
Population	425 patients with non-squamous or squamous NSCLC who have receive one or two previous cytotoxic treatments (one or more containing platinum-based combination therapies for stage IIIb or stage IV NSCLC	272 patients with advanced squamous NSCLC who have progressed following first line chemotherapy	582 patients with advanced non-squamous NSCLC who had progressed on platinum-based doublet-chemotherapy.	1034 patients with previously treated advanced NSCLC with a PD-L1 expression of greater than ≥1%
Intervention	Atezolizumab 1200mg 3 weekly	Nivolumab 3mg/kg every 2-weeks	Nivolumab 3mg/kg every 2-weeks	Pembrolizumab 2mg/kg 3-weekly Pembrolizumab 10mg/kg 3-weekly
Comparison	Docetaxel 75mg/kg^2 3-weekly	Docetaxel 75mg/kg^2 3-weekly	Docetaxel 75mg/kg^2 3-weekly	Docetaxel 75mg/kg^2 3-weekly
Key results	• Median follow-up: 21 months • Median PFS: Intervention 2.8 months vs comparator 4.0 months • Hazard ratio PFS: 0.95 (95%CI 0.82 – 1.10) • Median OS: Intervention 13.8 months (95%CI 11.8-15.7) vs comparator 9.6 months (95%CI 8.6-11.2) • Hazard ratio OS 0.73 (95%CI 0.62-0.87) • Median duration of treatment: Intervention 3.4 months vs comparator 2.1 months	• Minimum follow-up: 11 months • Median PFS: Intervention 3.5 months vs comparator 2.8 months • Hazard ratio: PFS: 0.62 95%CI0.47-0.81) • Median OS: Intervention 9.2 months (95%CI 7.3-13.3) vs comparator 6 months (95%CI 5.1-7.3) • Hazard ratio OS 0.59 (95%CI 0.44-0.79)	• Minimum follow-up: 13.2 months • Median PFS: Intervention 2.3 months vs comparator 4.2 months • Hazard ratio: PFS 0.92 (95%CI 0.77-1.11) • Median OS: Intervention 12.2 months vs comparator 9.4 months • Hazard ratio OS 0.73 (95%CI 0.59-0.89)	• Median follow-up: 13.1 months • Median PFS: Intervention 3.9 months (2mg/kg) 4.0 months (10mg/kg) vs comparator 4.0 moths • Hazard ratio: PFS: 0.85 (95%CI 0.73-0.98) • Median OS: Intervention 10.4 months (2mg/kg), 12.7 months (10mg/kg) vs comparator 8.5 months • Hazard ratio OS 0.67 (95%CI 0.56 – 0.80) • Median duration of treatment: Intervention 3.5 months (2mg/kg and 10mg/kg) vs comparator 2.0 months
Adverse events	• All adverse events: Intervention 94% vs comparator 96% • Grade 3-4 adverse events: intervention 37% vs comparator 54% • Adverse events leading to discontinuation of therapy: intervention 8% vs comparator 19%.	• All adverse events: Intervention 58% vs comparator 85% • Grade 3-4 adverse events: intervention 7% vs comparator 55% • Adverse events leading to discontinuation of therapy: intervention 3% vs comparator 10%	• All adverse events: Intervention 69% vs comparator 88% • Grade 3-4 adverse events: intervention 10% vs comparator 54% • Adverse events leading to discontinuation of therapy: intervention 5% vs comparator 15%	• All adverse events: Intervention 63% (2mg/kg) 66% 10mg/kg) vs comparator 81% • Grade 3-5 adverse events: intervention 13% (2mg/kg), 16% (10mg/kg) vs comparator 35% • Adverse events leading to discontinuation of therapy: intervention 4% (2mg/kg), 5% (10mg/kg) vs comparator 10%

2.2 Review of Clinical Evidence

The Pharmacology and Therapeutics Advisory Committee (PTAC) and the Cancer Treatments Committee of PTAC (CaTSoP) have provided clinical advice on the use of ICIs in the treatment of metastatic NSCLC on several occasions. Their reviews have focused on the individual evidence of each ICI and its applicability to New Zealand, the consideration of a class effect, the current treatment paradigm of NSCLC in New Zealand and what the treatment paradigm could look like should an ICI be funded in New Zealand subject to various eligibility criteria.

2.2.1 Clinical evidence summary

Meeting records for all previous PTAC and CaTSoP discussions can be located by navigating the application tracker links for each proposal outlined below.

Table 8: Summary of clinical advice by agent

1L monotherapy	1L combination therapy	2L
Pembrolizumab	Pembrolizumab	Nivolumab
Atezolizumab	Atezolizumab	Pembrolizumab
		Atezolizumab

2.2.2 Summary of most recent clinical advice

In July 2020, Pharmac sought additional clinical advice from CaTSoP regarding the current landscape for ICIs in NSCLC. Clinical advice was specifically sought regarding the place of ICI in the New Zealand NSCLC treatment paradigm and appropriate funding criteria. Records from this agenda item can be found here.

Some key points from the meeting record are summarised below to reiterate the current clinical advice position and provide context to the subsequent assessment:

Current landscape

- The Subcommittee noted that the treatment paradigm for advanced NSCLC continues to evolve due to the number of new lung cancer treatment being developed
- Since the Subcommittee last reviewed the treatment paradigm in April 2019, no major new trials had been published regarding the efficacy of treatments in this patient population
- ESMO and ASCO guidelines support the use of an ICI (atezolizumab, nivolumab, pembrolizumab) in the treatment of first line or second line advanced NSCLC as a monotherapy or a combination therapy with chemotherapy depending on the patient and caner characteristics.

Consideration of class effect

- The Subcommittee considered that, based on the totality of currently available data, ICI treatments appear to provide the same (or similar) effect in the treatment of advanced NSCLC.
- The Subcommittee considered that pembrolizumab and atezolizumab have the strongest data for use in the first line setting and that data is comparable for atezolizumab, nivolumab and pembrolizumab in the second line setting
- The Subcommittee reiterated that based on the currently available evidence (across multiple trials and agents) the overall survival gain for NSCLC patients with anti PD1/anti PD-L1 agents was approximately 3 months irrespective of treatment line. The Subcommittee considered that to date it remained the case that published evidence for the use of anti PD-1/anti PD-L1 agents does not indicate there is a ‘tail’ of longterm survivors with advanced NSCLC.

- The Subcommittee considered that published data indicates that a higher expression of PD-L1 on tumour cells or surrounding immune stromal cells correlates to a higher response rate from ICI agents.
- The Subcommittee considered that although patients with high PD-L1 expression appear to benefit most, those with lower expression may also benefit, with a statistically significant and clinically meaningful improvement in overall survival.

Clinical efficacy and population eligibility characteristics

- The Subcommittee noted that while ICI treatments have less side effects than chemotherapy, a small proportion of patients who have ICI treatments will experience significant immune mediated adverse events which require intensive management, monitoring and treatment, often over a long period.
- The Subcommittee considered that the majority of research regarding the use of immunotherapies for lung cancer to date has been conducted in patients who do not express targetable driver mutations (e.g. EGFR-negative, ALK-negative). Therefore, the Subcommittee considered there continued to be a lack of data to support efficacy of anti PD-1/anti PD-L1 agents in patients with known driver mutations, such that inclusion of these populations in any funding criteria for anti PD-1/anti PD-L1 agents could not currently be supported.
- The Subcommittee considered it remained appropriate to limit patients to a single line of treatment with anti PD-1/anti PD-L1 agents which could be administered at any point in the treatment sequence for patients with EGFR wild-type or ALK-negative advanced NSCLC.
- The Subcommittee considered that it would be appropriate to limit the total duration for a course of anti PD-1/anti PD-L1 treatment for advanced NSCLC patients to a maximum of two years of continuous treatment. The Subcommittee considered that while it was expected there may be gaps in treatment due to adverse events, as with many oncology treatments, there was a lack of data to support retreatment following disease progression in anti PD-1/anti PD-L1 pre-treated NSCLC patients, and that treatment should cease at signs of disease progression (whether this occurred during continuous treatment or in a period when 'off' treatment).

PD-L1 expression and PD-L1 testing

- The Subcommittee considered that while there is variability between trials for anti PD1/anti PD-L1 agents (atezolizumab, pembrolizumab, durvalumab, nivolumab) in how they stratify by PD-L1 expression, participants are generally grouped based on PDL1 tumour expression of ≥ 50% (high expression), PD-L1 tumour expression of ≥ 1% (PD-L1 positive), and PD-L1 expression
- The Subcommittee considered that although stratification of patients in clinical trials based on PD-L1 expression is relatively consistent across studies, at the current time it is difficult to determine what the downstream immune effects of PD-L1 blockade are and so PD-L1 expression may not be biologically meaningful in defining a patient population for exclusion of benefit of anti PD-1/anti PD-L1 treatment.
- The Subcommittee considered that use of different assays, tumour proportion scores, and PD-L1 expression thresholds may lead to problems with reproducibility and standardisation of testing and by extrapolation the benefits observed in trial populations. The Subcommittee considered that lab-developed tests used in New Zealand may not have the same sensitivity as the tests used in the clinical trials. As a variety of PD-L1 testing platforms are in use in New Zealand, the Subcommittee considered that the true rates of PD-L1 expression in NSCLC for patients in New Zealand may be difficult to estimate.
- The Subcommittee considered that lab-developed tests used in New Zealand may not have the same sensitivity as the tests used in the clinical trials. As a variety of PD-L1 testing platforms are in use in New Zealand, the Subcommittee considered that the true rates of PD-L1 expression in NSCLC for patients in New Zealand may be difficult to estimate.

- The Subcommittee considered there were benefits and shortfalls of a Special Authority criteria mandating PD-L1 testing to determine eligibility for anti PD-1/anti PD-L1 agents for advanced NSCLC.

Special Authority and other funding considerations

- The Subcommittee considered that, while funding for all advanced NSCLC would be the preferred outcome, if targeting was required for fiscal reasons, then use of PD-L1 expression would be reasonable.
- The Subcommittee considered that, if anti PD-1/anti PD-L1 agents were to be funded in New Zealand, subject to criteria irrespective of PD-L1 expression (i.e. where PDL1 level did not determine eligibility for funding) that this would allow clinicians to prescribe anti PD-1/anti PD-L1 agents according to patient needs and clinical judgement. The Subcommittee considered that in this situation it was likely that the majority of patients would receive treatment as a combination regimen with chemotherapy, and only those considered unfit for chemotherapy would likely receive monotherapy.
- The Subcommittee considered that, conversely, if anti PD-1/anti PD-L1 agents were to be funded in New Zealand subject to criteria that mandated PD-L1 expression (i.e. where PD-L1 level was a required determinant of eligibility for funding) use of a 50% threshold would likely be appropriate. The Subcommittee considered that this could target funded treatment to those that may benefit most and limit the overall resource impact for DHBs.
- The Subcommittee considered that if first-line treatment were to be funded for all advanced NSCLC patients (rather than only a high PD-L1 expression population), PDL1 level would likely be used to determine treatment regimen. The Subcommittee considered that any patients whose disease had high PD-L1 expression (50% or greater) would likely receive anti PD-1/anti PD-L1 monotherapy, with patients whose disease had PD-L1 expression less than 50% who are 'fit' receiving the combination regimen. The Subcommittee considered that in this scenario patients who are 'unfit' to receive chemotherapy and did not have disease with high expression of PD-L1 may not be eligible to receive funded anti PD-1/anti PD-L1 treatment.
- The Subcommittee considered that mandating PD-L1 testing would require DHBs to fund and provide tests but may create inequities for patients who are unfit for chemotherapy and may not meet the specified PD-L1 expression threshold.
- The Subcommittee considered that if PD-L1 testing was not used to specify eligibility for funding, it was uncertain whether testing would be implemented equitably by DHBs. The Subcommittee considered this may result in more patients receiving combination chemotherapy regimens with the additional toxicities and resourcing requirements when comparable benefit could likely be achieved without this.
- The Subcommittee considered that, given these points, it would be reasonable to progress funding for anti PD-1/anti PD-L1 agents in the treatment of advanced NSCLC subject to criteria with or without specification of PD-L1 based on assessment of the most favourable cost-effectiveness taking in to account the health system impacts.
- Proposed special authority criteria:

PD-L1 defined population

Initial application - (NSCLC first-line) only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1. Patient has not received prior treatment with an immune checkpoint inhibitor for non-small cell lung cancer (NSCLC); and
2. Either:
   2.1. All of the following:
      2.1.1. Patient has locally advanced or metastatic, unresectable, NSCLC; and

2.1.2. The patient has not had prior chemotherapy treatment for their disease; and
2.1.3. There is documentation confirming that the disease does not express driver mutations of EGFR or ALK tyrosine kinase; and
2.1.4. There is documentation confirming the disease expresses PD-L1 at a level of equal or greater than 50% as determined by a validated diagnostic test; and
2.1.5. Patient has an ECOG 0-1; and
2.1.6. Patient does not have uncontrolled brain metastases; and
2.1.7. [Chemical] to be used as monotherapy at a maximum dose of [dose] for a maximum of 12 weeks; and
2.1.8. Baseline measurement of overall tumour burden is documented; or

2.2. All of the following:
2.2.1. Patient has metastatic, unresectable, NSCLC; and
2.2.2. The patient has not had prior treatment for their metastatic disease; and
2.2.3. There is documentation confirming that the disease does not express driver mutations of EGFR or ALK tyrosine kinase; and
2.2.4. Patient has an ECOG 0-1; and
2.2.5. Patient does not have uncontrolled brain metastases; and
2.2.6. [Chemical] to be used in combination with chemotherapy at a maximum dose of [dose] for a maximum of 12 weeks; and
2.2.7. Baseline measurement of overall tumour burden is documented.

Initial application- (NSCLC second-line) only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1. Patient has locally advanced or metastatic non-small cell lung cancer (NSCLC); and
2. There is documentation confirming that the disease does not express driver mutations of EGFR or ALK tyrosine kinase; and
3. Patient has an ECOG 0-1; and
4. Patient does not have uncontrolled brain metastases; and
5. Patient has documented disease progression following treatment with platinum-based chemotherapy; and
6. Patient has not had prior treatment with immune checkpoint inhibitors for NSCLC; and
7. [Chemical] is to be used as monotherapy at a dose of [dose] for a maximum of 12 weeks; and
8. Baseline measurement of overall tumour burden is documented as per RECIST criteria.

Renewal – (NSCLC first or second-line) only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following

1. Any of the following:
   1.1. Patient's disease has had a complete response to treatment according to RECIST criteria; or
   1.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
   1.3. Patient has stable disease according to RECIST criteria; and
2. Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3. No evidence of disease progression according to RECIST criteria; and
4. The treatment remains clinically appropriate and patient is benefitting from treatment; and
5. [chemical] to be used at a maximum dose of [dose] (or equivalent); and
6. [chemical] to be discontinued at signs of disease progression; and
7. Treatment with [chemical] to cease after a total duration of 24 months from commencement.

Irrespective of PD-L1 (regimen/dose not defined either)

Initial application - (NSCLC first-line) only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1. Patient has not received prior treatment with an immune checkpoint inhibitor for non-small cell lung cancer (NSCLC); and
2. Patient has locally advanced or metastatic, unresectable, NSCLC; and
3. The patient has not had prior chemotherapy treatment for their disease; and
4. There is documentation confirming that the disease does not express driver mutations of EGFR or ALK tyrosine kinase; and
5. Patient has an ECOG 0-1; and
6. Patient does not have uncontrolled brain metastases; and
7. Baseline measurement of overall tumour burden is documented.

Initial application- (NSCLC second-line) only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following:

1. Patient has locally advanced or metastatic non-small cell lung cancer (NSCLC); and
2. There is documentation confirming that the disease does not express driver mutations of EGFR or ALK tyrosine kinase; and
3. Patient has an ECOG 0-1; and
4. Patient does not have uncontrolled brain metastases; and
5. Patient has documented disease progression following treatment with platinum-based chemotherapy; and
6. Patient has not had prior treatment with immune checkpoint inhibitors for NSCLC; and
7. Baseline measurement of overall tumour burden is documented as per RECIST criteria.

Renewal – (NSCLC first or second-line) only from a medical oncologist or any relevant practitioner on the recommendation of a medical oncologist. Approvals valid for 3 months for applications meeting the following criteria:

All of the following

1. Any of the following:
   1.1. Patient's disease has had a complete response to treatment according to RECIST criteria; or
   1.2. Patient's disease has had a partial response to treatment according to RECIST criteria; or
   1.3. Patient has stable disease according to RECIST criteria; and
2. Response to treatment in target lesions has been determined by radiologic assessment (CT or MRI scan) following the most recent treatment period; and
3. No evidence of disease progression according to RECIST criteria; and
4. The treatment remains clinically appropriate and patient is benefitting from treatment; and
5. [Chemical] to be discontinued at signs of disease progression; and
6. Treatment with [chemical] to cease after a total duration of 24 months from commencement.

3. Supplier and International Cost-Utility Analyses

3.1 Cost-Utility Analysis in Application

Error! Reference source not found. below summaries the cost-utility analyses provided by the supplier or applicants for all proposals being considered in the TAR. Given the complexities of modelling multiple different pharmaceuticals that were considered by PTAC and CaTSoP to have the same or similar clinical effect, a decision was made to create a Pharmac cost-utility model that could appropriately evaluate the cost-effectiveness of the various different funding scenarios it may wish to consider in the NSCLC treatment paradigm.

3.2 International Cost-Utility Analyses

Table 10 and

Table *11* below summaries the key considerations of the cost-utility analysis reviewed by NICE in England/Wales and PBAC in Australia. International reviews included in this table are limited to those that relate to proposals with a positive clinical advice recommendation by PTAC and CaTSoP.

Table 9- Summary of cost-utility analysis provided by the supplier/applicant

ICI	Date	CUA result	Scope	Probabilities	HR-QOL	Costs	Other
First line monotherapy PD-L1 >50%.							
Atezolizumab	**Feb 2020**	S 9 QALYS per million dollars spent	• PICO as per trial evidence • Lifetime model Markov model	• IMpower110 for first line transition probabilities. • Comparator arm of IMpower110 used for second line transition probabilities in comparator arm of model • Included consideration of patient proportion who had no second line treatment • Transition probabilities from progressed disease health state from Shepard et al, 2000 Docetaxel study. Exponential distribution used for extrapolation of all parameters	• Trial HR-QOL data not available • Sourced from Parache et al 2018. (systematic review) • 0.77 PFS 1 • 0.66 PFS 2 • 0.40 PD Disutility from adverse events incorporated	Pharmaceutical • Atezolizumab • Chemotherapy agents (cisplatin, pemetrexed, docetaxel, gemcitabine) • Peg-filgrastim for neutropenia management Other costs • infusion costs management of grade 3-4 adverse events	Cost of PD-L1 testing not considered
Pembrolizumab	**Jan 2017**	S 9 QALYS per million dollars spent	• PICO as per trial evidence • Lifetime model Cohort simulation model	• Keynote024 time on treatment data used for first line transition probabilities. • PFS pembrolizumab extrapolated with Weibull function, PFS standard of care extrapolated with an exponential function • OS pembrolizumab and Standard of care extrapolated with exponential function Subsequent therapies included	• HR-QOL data from KN024 • Time to death approach used S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2) S 9(2)(b)(ii), 9(2)(ba)(i) & 9 S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)	Pharmaceutical • Pembrolizumab • Chemotherapy (gemcitabine, paclitaxel, carboplatin, Other costs • PD-1 testing • Infusion costs • Weekly disease management cost of $190 – both arms • Progressed disease management costs $170 weekly – both arms • ED care cost – one-off • Terminal care costs • Adverse event management cost	• 2-year maximum treatment duration considered Appears to include pembrolizumab as subsequent therapy

First line combination therapy							
Pembrolizumab	**Aug 2018**	S 9 QALYS per million dollars spent	• Partition survival analysis • Life-time horizon • PICO as per trial evidence	• Keynote189 primary source of data • PFS modelled using time on treatment data. Both intervention and comparator were extrapolated with Weibull functions. • OS - Both intervention and comparator were extrapolated with Weibull functions. OS adjusted for cross-over All cause grade 3 and 4 adverse events included	• Sourced from ED-5D-3L data collected from Keynote-189 • Time to death approach used S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	Pharmaceuticals • Pembrolizumab • Chemotherapy (carboplatin, cisplatin, docetaxel, pemetrexed) • Infusion, Pre-medication Other costs • Infusion costs • Progressed disease monitoring cost • Progression free disease monitoring cost • Terminal care cots Adverse event management	2-year pembrolizumab treatment duration considered
Second Line							
Atezolizumab	**May 2017**	S 9 QALYS per million dollars spent	• PICO as per trial evidence • Lifetime model (20 years) Markov model	• Oak trial primary source of data All probabilities extrapolated using exponential curves. Where appropriate curves were broken into two separate exponentials to increase fit.	• Sourced from Chouaid et. 2013 PFS 0.70, PD, 0.58	Pharmaceuticals • Atezolizumab • Docetaxel Other costs • Infusion costs	• Supportive care cost with treatment not included as they were considered similar between both arms of the model • No adverse event management cost included as it was considered nominal to the total costs incurred No PD-L1 testing included
Nivolumab	**Feb 2016**	S 9 QALYS per million dollars spent (weighted - both histologies)	• PICO as per trial evidence • 10-year time horizon	• CA209-017 (squamous NSCLC) and CA209-057 (non-squamous NSCLC). Primary source of data • Mixture of extrapolation functions used for PFS and OS including exponential, Weibull and log-logistic.	• EQ-5D-5L data from trial used S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	Pharmaceutical costs • Nivolumab • Docetaxel Other costs • Infusion costs PFS and PD management costs weighted by time in state	• Adverse event not incorporated – considered a conservative assumption given the claim of superior safety (supplier justification) • Subseuqnet chemotherapy not included considered to be same or similar in both arms No PD-L1 testing considered

Pembrolizumab	**Sep 2016**	S 9 QALYS per million dollars spent	• Partition survival analysis • Life-time horizon • PICO as per trial evidence	• Keynote010 primary source of data • PFS for intervention modelled from PFS Kaplan Meir curves fitted with a Weibull function. PFS for comparator fitted with exponential distribution. • OS for comparator modelled using Kaplan Meir curves than extrapolated with exponential functions Subsequent treatment modelled as per clinical trial	• Sourced from ED-5D-3L data collected from Keynote-189 • Time to death approach used S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) Disutility for adverse events also considered	Pharmaceutical costs • Pembrolizumab • Docetaxel • Docetaxel pre/contaminant medications Other costs • PD-1 testing • Infusion administration • PFS management costs $149 per week in intervention and $155 in comparator • PD management costs $112 per week • Terminal care costs Adverse event management costs	None noted

Table 10: Summary of second-line technology appraisals from NICE and PBAC

ICI second line, metastatic NSCLC			
	Atezolizumab	**Nivolumab**	**Pembrolizumab**
PBAC (Australia)	PSD November 2019 – **update dosing recommended** PSD November 2017 **Recommended** for funding based on atezolizumab being non-inferior in effectiveness and safety with nivolumab which is current listed.	March 2019 – **update dosing recommended** March 2017 – **recommended** (histologies combined)) • Updated submission and risk sharing agreement proposed in the resubmission were considered acceptable November 2016 – **deferred** (SQ PSD, NSQ PSD) • Economic model compared to pemetrexed using an indirect comparison considered unreliable. Economic model compared to docetaxel has a high incremental cost per QALY but that this was acceptable with a risk share agreement providing the supplier addressed concerns regarding the effectiveness of nivolumab in those aged 75+ who have a high clinical need. (NSQ) March 2016 – **rejected** (SQ PSD, NSQ PSD)	PSD November 2016 – rejected - proposal for PDL1>50%
NICE (England and Wales)	TA520 May 2018 **Recommended** as a treatment option following chemotherapy for EGFR, ALK wildtype NSCLC patient's conditional on two-year maximum treatment duration and discounted patient access scheme Considerations: • PICO was noted as appropriate – two PICO's one for PDL1 positive patients with pembrolizumab as the comparator and one for PDL1 negative patients with docetaxel as the comparator (OAK trial) • CUA for PDL1 positive population was in the range considered cost-effective to NHS resources. CUA for PDL1 negative population was considered to meet NICE's end of life treatment criteria and considered it to within the range deemed cost-effective to NHS resource • Modelling considerations: 5-year time horizon considered more appropriate than lifetime, OS benefit considered, uncertainty in extrapolation of OS – log-logistic used, 2-year treatment duration maximum assumed	TA484 November 2017 (non-squamous) **Recommended** as a treatment option following chemotherapy for EGFR, ALK wildtype NSCLC patients who are PDL1 positive, conditional on two-year maximum treatment duration and a managed access agreement Considerations: • PICO noted as appropriate – CheckMate057 primary source of data. Sensitivity analysis compared to BSC as not all will be fit for docetaxel • Modelling considerations: exponential used to extrapolate PFS and OS, utility of 0.569 in PD and 0.713 in PFS accepted as appropriate. Consideration that a treatment benefit may be sustained beyond treatment cessation. TA655 October 2020 (squamous) **Recommended** as a treatment for metastatic NSCLC following chemotherapy conditional on a 2-year treatment duration, no previous ICI use and a commercial arrangement. Considerations: • PICO noted as appropriate – CheckMate017 primary source of data • Change in dosing from weight-based to a fixed dose noted as already being part of clinical practice – equal efficacy assumed • Using the committee's preferred assumptions of 2-year treatment duration and 3-years of subsequent survival benefit, the most plausible ICER was S 9(2) per QAYS S QALYs per million NZD spent).	TA428 Jan 2017 **Recommended** as a treatment option following chemotherapy for EGFR, ALK wildtype NSCLC patient's conditional on two-year maximum treatment duration and commercial access agreement Considerations: • PICO was noted as appropriate – KEYNOTE-010. Pembrolizumab compared with docetaxel • Model noted to be sensitive to treatment effect continuing after ceasing treatment but with a 2-year stopping rule concluded that majority of plausible ICERS were below the range considered a cost-effective use of NHS resources • Modelling considerations: 2-year time horizon, OS extrapolated as an exponential, uncertainty in difference/relationship between time to treatment duration and PFS, control for crossover in trial

Table 11: Summary of first-line technology appraisals from NICE and PBAC

ICI first line, metastatic NSCLC			
	Atezolizumab monotherapy	**Pembrolizumab monotherapy**	**Pembrolizumab combination therapy**
PBAC (Australia)	No evidence of PBAC assessing this proposal could be found at the time of writing this TAR.	PSD July 2018 **Recommended** as a treatment for those with PD-L1>50% metastatic NSCLC with no prior treatment for their metastatic disease. Considerations: • Cost-effectiveness and budget impact considered acceptable for this defined patient population • Offset with nivolumab no longer accessed in 2L for some patients considered PSD March 2018 – deferred PSD November 2017 – deferred PSD March 2017 – rejected	PSD July 2019 – **recommended** – NSQ in combination with chemotherapy Two analysis: 1) PDL1< 50% - comparator was chemotherapy then a ICI inhibitor, considered to show a significant improvement in efficacy, PDL1>50% pembrolizumab monotherapy followed by platinum doublet - Cost-effectiveness considered acceptable at the proposed price and that the cost per treatment duration was similar to already funded therapies including pembrolizumab monotherapy. PSD November 2018 – rejected
NICE (England and Wales)	TA in development – expected publication June 2021	TA531 July 2018 **Recommended** as an option for untreated PD-L1 positive metastatic NSCLC with a PD-L1 expression of 50% or greater with no EGFR or ALK mutations for a treatment duration of 2-years Considerations: • PICO appropriate – KEYNOTE 024 • Treatment benefit beyond treatment cessation was considered plausible but uncertain • The utility values reported from KEYNOTE-024 were considered implausible as were in cases higher than UK population norms and utility caps of UK population norms were recommended.	TA600 September 2019 – SQ **Recommended** for funding within the Cancer Drugs Fund when used in combination with carboplatin and paclitaxel for the treatment of untreated metastatic squamous NSCLC if treatment is stopped after 2-years of uninterrupted treatment. Considerations: • Keynote407 • Cost-effectiveness was considered uncertain due the immaturity of clinical evidence. • Pembrolizumab standard of care in PDL1>50% patients indirect comparison required • NICE considered that the true benefit of subsequent lines of treatment including immunotherapies was not full captured in the model to align with current clinical practice • Uncertainty in OS extrapolation TA557 March 2021 – NSQ **Recommended** for funding in the Cancer Drug Fund for patients who are EGFR and ALK mutation negative only if treatment is for 2-years. Considerations: • Keynote189 • Same modelling considerations as TA600 above.

4. Pharmac Cost-Utility Analyses

Two cost-utility models were developed by Pharmac staff to evaluate the cost-effectiveness of ICI for patients with locally advanced or metastatic lung cancer (EFGR and ALK mutation wild-type). The first model considers the cost-effectiveness of funding an ICI for use in a first line setting while the second model considered the cost-effectiveness of funding an ICI in a second line setting.

Several different cost-utility analyses were run though the two models to represent the cost-effectiveness of various possible funding scenarios as outlined previously in this TAR (Proposals A-F outlined in Section 1.1 above and illustrated in Figure 2). Generating the cost-effectiveness results for each scenario involved running each model separately and where appropriate, combining them using a patient number weighted approach. Each model is described below; the specific inputs/assumptions, cost-effectiveness results and scenario analysis are then presented for each scenario.

4.1 Scope of Analysis

The analysis was undertaken from the perspective of the funder, with regards to Pharmac's Factors for Consideration.

4.1.1 Target Population and PICOs

The intended target population for ICI therapy is patients with locally advanced or metastatic lung cancer who do not have an EGFR or ALK mutation.

The PICO statements for each proposal and the treatment paradigm change considered in each PICO is outlined in detail in Section 1.1 of the TAR and illustrated in Figure 2.

4.2 Model Structure

Two separate Markov models were constructed. The first model considered the funding of an ICI as a first line therapy and permitted consideration of an ICI should it be funded as a first-line monotherapy for those with a PD-L1>50%, as a combination therapy with chemotherapy regardless of PD-L1 status or a combination of both. The second model considered the funding of an ICI as a second line therapy. The structure of each model is outlined in turn below.

4.2.1 Time Horizon

The Markov cycle length for both models was weekly. The time-horizon of the first line model and second line model as 20-years. All costs and benefits were discounted at 3.5%.

4.2.2 First line locally advanced or metastatic NSCLC model (EGFR and ALK wildtype)

The intervention arm of the 1L model has nine health states:

- ICI monotherapy (ICI mono)
- ICI in combination with chemotherapy non-squamous histology (ICI chemo NSQ)
- ICI in combination with chemotherapy squamous histology (ICI chemo SQ)
- Chemotherapy squamous histology (Chemo SQ)
- Chemotherapy non-squamous histology (Chemo NSQ)
- Docetaxel
- Best supportive care (BSC)
- Progressed disease

- Dead

The comparator arm of the 1L model has six health states:

- Chemotherapy squamous histology (Chemo SQ)
- Chemotherapy non-squamous histology (Chemo NSQ)
- Docetaxel
- Best supportive care (BSC)
- Progressed disease
- Dead

The following paragraphs describe how the first line model works. Markov tree diagrams displayed in Figure 3 (Intervention arm first line monotherapy), Figure 4 (intervention arm first line combination therapy) and Figure 5 (comparator arm) below graphically illustrate the model.

Model Start

Depending on the scenario being modelled, the modelled cohort can start in any of the three health states where an immune checkpoint inhibitor is specified ('ICI monotherapy', 'ICI chemo NSQ', 'ICI chemo SQ'). The model contains a variable to allow for the proportion of the cohort receiving ICI therapy as monotherapy or in combination with chemotherapy to be varied as required (See section titled "Probability of starting the model in ICI monotherapy vs ICI with chemotherapy" below for more information). Another variable ensures the proportion of the modelled cohort who are to have ICI therapy in combination with chemotherapy are split between the corresponding non-squamous (NSQ) and squamous (SQ) health states as the prevalence of each histology dictates (75% non-squamous, 25% squamous). The separation of ICI therapy by histology type was necessary to represent key differences in the chemotherapy treatment regimens.

ICI Monotherapy

Figure 3 below illustrates the intervention arm of the first line model and highlights the relevant health states that are utilised in the modelling of first line ICI monotherapy. All transition probabilities are described in turn in section 4.3 below and summarised in Table 12.

The modelled cohort begins the model in the 'ICI monotherapy' health state and have a weekly probability of remaining in the health state, progressing or dying. If progression occurs, a subsequent decision fork determines whether a second line treatment is indicated. If the decision variable specifies a second line treatment is available, then the second model fork determines what proportion have non-squamous or squamous histology to allow the appropriate proportions of the model cohort to progress to the NSQ chemotherapy or SQ chemotherapy health states. As stated above, this distinction is necessary due to key difference in chemotherapy regimens between histologies. If the model decision variable specified at the first decision fork deems no second line treatment is to occur, then the relevant cohort progresses to the best supportive care health state. In the model base case, 100% of patients progress to second line treatment following ICI monotherapy.

A similar event series occurs for the model cohort who have progressed to the 'NSQ chemo' and 'SQ chemo' health states. Every model cycle, there is a probability to remain in the health state, progress or die. If progression is to occur, a decision fork and a decision variable allow for a decision to be made on whether a third line treatment, docetaxel, is indicated. In the model base case 50% of the cohort progresses to receive docetaxel with the remaining 50% progressing to the 'best supportive care' health state. The model cohort in both the docetaxel and best supportive care health state can either remain, progress, or die each cycle. Progression from either health state representing the end of the treatment paradigm and a transition to the progressed disease health state. From the progressed disease health state, the modelled cohort can remain in the health state or die.

ICI in combination with chemotherapy

Figure 4 below illustrates the intervention arm of the first line model and highlights the relevant health states that are utilised in the modelling of first line ICI in combination with chemotherapy. All transition probabilities are described in turn in section 4.3 below and summarised in Table 12.

The two relevant health states for the proportion of the model cohort having first line treatment with ICI therapy in combination with chemotherapy are 'NSQ ICI with chemo' and 'SQ ICI with chemo'. The two states represent the different chemotherapy treatment regimens associated with each histology when used in combination with ICI. In both health states, there is a probability in each model cycle to remain in the health state, progress or die. If progression is to occur, a subsequent decision fork and decision variable decides whether a subsequent line of therapy, docetaxel is indicated. If another line of therapy is indicated, then that proportion of the model cohort progresses to the 'docetaxel' health state. For the proportion where no further therapy is indicated, transition to the 'best supportive care' health state occurs. From both the 'docetaxel' and 'best supportive care' health state, the model cohort can remain in the health state, progress to progressed disease or die. The 'progressed disease' health state represents the end of available treatment and is a state in which the only options are to remain or die.

Comparator arm

Figure 5 illustrates the comparator of the 1L model. The treatment paradigm represented is platinum-based chemotherapy for either squamous or non-squamous histology as appropriate, followed by docetaxel. The patient flow through the health states is the same as the corresponding health states in the intervention arm of the model described above. All transition probabilities are described in turn in section 4.3 below and summarised in Table 12.

Figure 3: 1L model, Intervention arm depicting ICI monotherapy

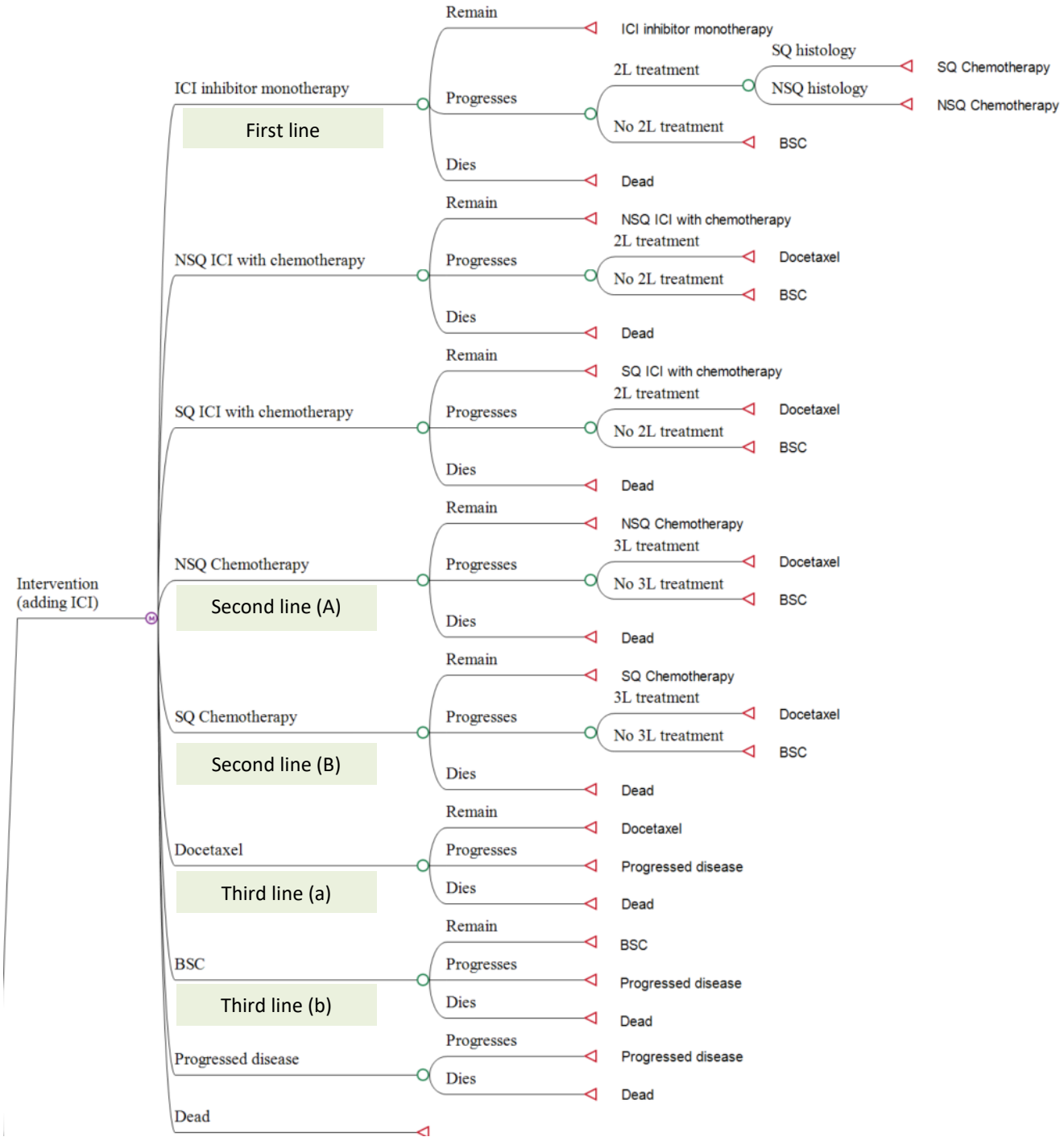
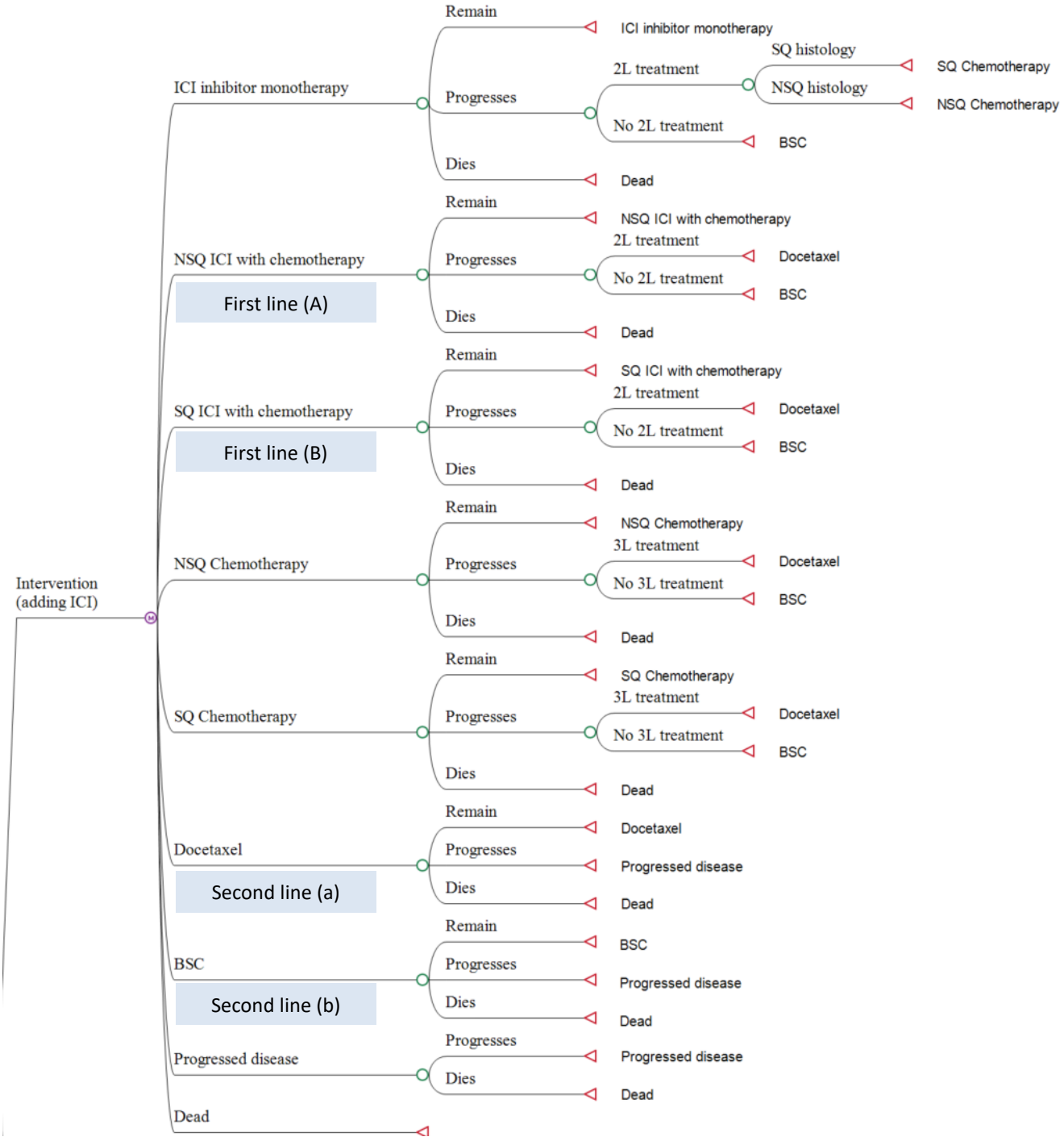


Figure 4: 1L model, Intervention arm depicting ICI in combination with chemotherapy



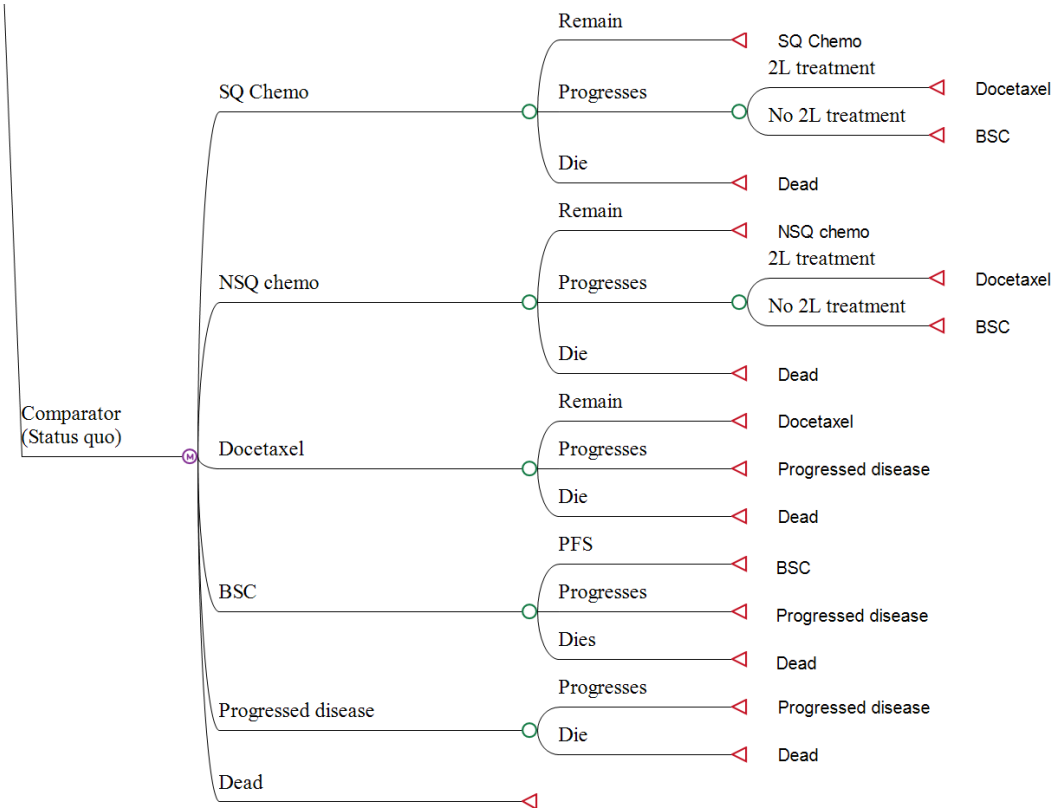


Figure 5: 1L comparator arm.

4.2.2 Second line locally advanced or metastatic NSCLC model (EGFR and ALK wildtype)

A branch of the second line Markov model can be found below (Figure 6). The model compares an ICI with docetaxel. All transition probabilities are described in turn in section 4.3 below and summarised in Table 15.

The immune checkpoint inhibitor arm of the model has five health states:

- PFS1 immune checkpoint inhibitor
- PFS2: Docetaxel
- PFS3: best supportive care (BSC)
- Progressed Disease
- Dead.

All patients begin the model in the PFS1 ICI state and have a weekly probability of remaining in the PFS health state, having disease progression or death. Upon disease progression in the PFS1 health state, an additional transitional probability is applied to decide whether a subsequent treatment of docetaxel will occur or if the patient progresses to the non-treatment state of best supportive care. In both the PFS2 and best supportive care health states, there is a weekly probability of remaining in PFS, disease progression and movement to the progressed disease health state or death. Similarly, from the progressed disease health state, there is a weekly probability of remaining in this state or death.

The comparator arm of this model has the following five health states:

- PFS1 docetaxel
- Progressed disease 1: docetaxel
- PFS2 best supportive care
- Progressed disease 2: best supportive care
- Dead

The model cohort starts in PFS1 or PFS2, with the proportion in each determined by the number of people who are expected to receive docetaxel therapy (50% in the base case).

The proportion of the cohort starting in the model in 'PFS1 docetaxel' have a probability each cycle of remaining in the health state, progressing to 'progressed disease 1: docetaxel' or dying. Once in the 'progressed disease 1: docetaxel', the modelled cohort have a probability each cycle of remaining in a state of PFS or dying.

The proportion of the cohort starting in the model in 'PFS2 BSC' have a probability each cycle of remaining in the health state, progressing to 'progressed disease 2: BSC. Once in 'progressed disease 2: BSC, the modelled cohort have a probability each cycle of remaining in a state of PFS or dying.

This model structure is intended to capture the fact that the probability of progression and death is likely to be different for those patients who are fit enough to have docetaxel and those who are not fit enough or are not able to take docetaxel. The trial data for ICI agents compared to docetaxel, does not capture the experience of those patients who do not have docetaxel, so a separate patient flow of health states was required.

Note: For the first line model and the intervention arm of the 2L model, the trial data used did not exclude patients who used docetaxel as a subsequent therapy line, so the OS data captured in these trials was considered representative of both those who could have and those who did not have docetaxel. The 1L and 2L intervention arm have a BSC health state which represents the progression experience of the modelled cohort if they are unable to take docetaxel.

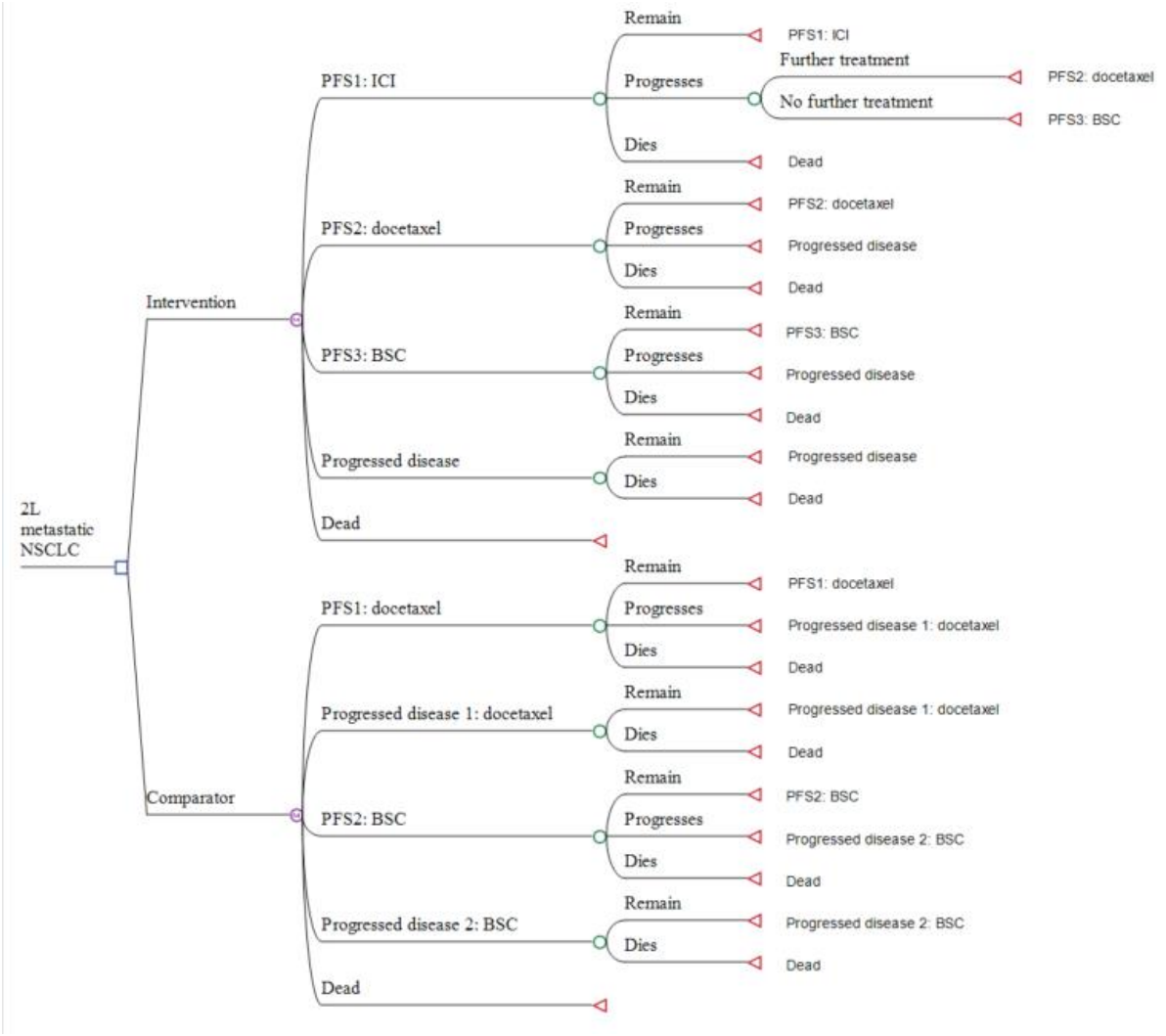


Figure 6: 2L model structure

4.3 Transformation and Extrapolation of Clinical Evidence

4.3.1 Clinical Parameter Estimates

First line model (by health state)

First line ICI monotherapy - Probability of progression and death (intervention arm only)

At the time of analysis pembrolizumab and atezolizumab were the only ICI agents with a positive clinical advice recommendation for use as a first line monotherapy. As the atezolizumab trial, IMpower110, was yet to be published in a peer-review journal, the transition probabilities in the model relating to the ICI monotherapy first line treatment were therefore derived from the pivotal trial for pembrolizumab in this setting, KEYNOTE-024. This decision was further justified by the similar hazard ratios for death between the two trials and clinical advice summarised early in this TAR that the agents are likely to have the same or similar theraputic effect. The hazard ratio for death published in a conference abstract from IMPower110 was noted to be 0.595 (95%CI 0.398-0.890) while the hazard ratio for death in KEYNOTE-024 was similar 0.60 (95%CI, 0.41 to 0.89)). No PFS data from IMpower 110 was available at the time of the assessment. Pharmac staff will reconsider this assumption following the publication of IMpower110 in a peer-reviewed journal.

Figure 7 show the PFS curve from KEYNOTE-024. The first 9 months of the Kaplan Meier line for pembrolizumab was plot digitized. In order to increase the goodness of fit, two separate exponentials were plotted to determine the monthly transition probability. One transition probability was calculated for the first 5-months of data while the subsequent transition probability represented the second 5-months of data. The monthly probabilities were transformed into a weekly probability in TreeAge using the 'probtoprob' function. The monthly transition probability for ICI monotherapy PFS was 0.094 for the first 5-months and 0.059 thereafter.

Figure 8 shows the OS curve from KEYNOTE-024 that was used to determine the transition probability for first line monotherapy pembrolizumab. The longer-term follow-up data published in 2019 by Reck et al was used. The first 24 months of the Kaplan Meier line for pembrolizumab was plot digitized and fitted with an exponential curve to determine the monthly transition probability. The monthly probability was transformed into a weekly probability in TreeAge using the 'probtoprob' function. The monthly transition probability for ICI monotherapy OS was 0.029.

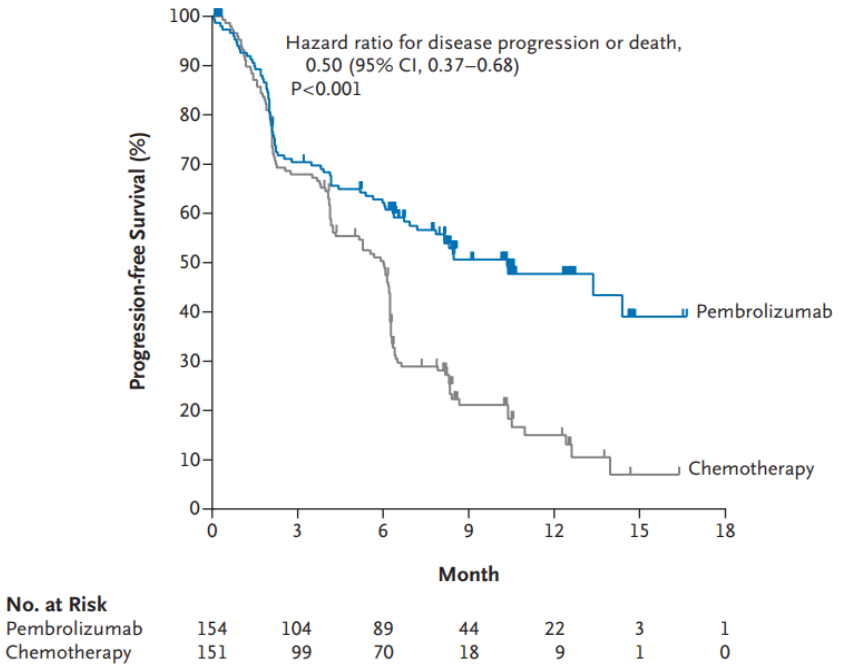


Figure 7: Kaplan-Meier PFS curve (ITT population) KEYNOTE-024 (2016)

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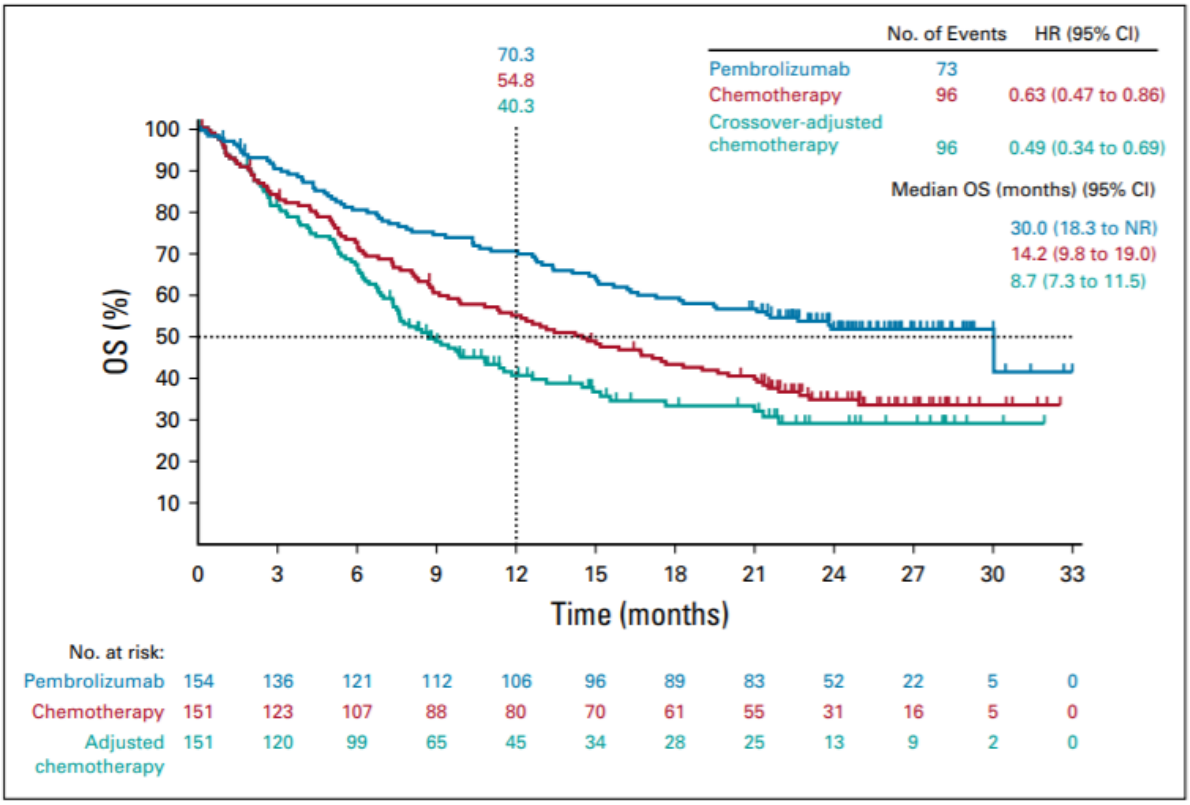

Figure 8: Kaplan-Meier OS curve (ITT population) KEYNOTE-024- updated analysis (2019)

First line ICI in combination with chemotherapy (NSQ) – probability of progression and death (intervention arm only)

At the time of analysis, pembrolizumab was the only ICI agent with a positive clinical advice recommendation for use as a first line therapy in combination with chemotherapy. The transition probabilities in the model relating to the ICI in combination with chemotherapy NSQ first line where therefore derived from the pivotal trial for pembrolizumab in this setting, KEYNOTE-189.

Figure 9 shows the PFS curve from KEYNOTE-189 that was used to determine the transition probability for first line ICI in combination with chemotherapy with NSQ histology. The first 14 months of the Kaplan Meier line for pembrolizumab combination was plot digitized and fitted with an exponential curve to determine the monthly transition probability. The monthly probability was transformed into a weekly probability in TreeAge using the 'probtoprob' function. The monthly transition probability for ICI in combination with chemotherapy NSQ PFS was 0.079.

The transition probability is based on the Kaplan Meier curve for the study population irrespective of PD-L1 status. Although the rate of progression appears to decrease as PD-L1 expression increases, the clinical advice recommendation at the time of analysis was that if an ICI for use in combination therapy was funded in the first line, no PD-L1 expression would be required to access the treatment. The trial data concerning the study population as a whole was therefore considered most relevant to inform the transition probability for an ICI in combination with chemotherapy.

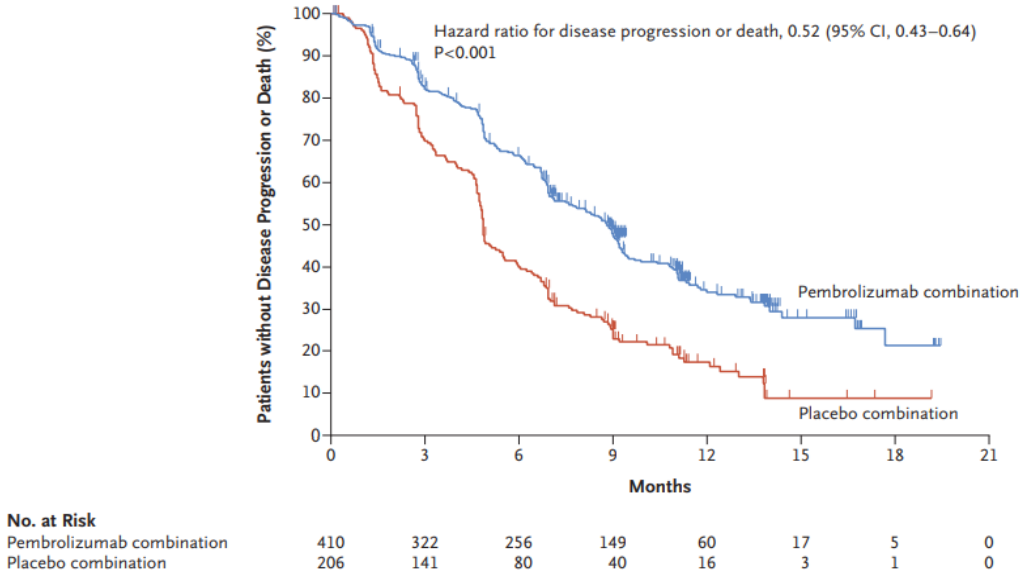

Figure 9: Kaplan-Meier PFS curve (ITT population) KEYNOTE-189

Figure 10 shows the OS curve from KEYNOTE-189 that was used to determine the transition probability for first line ICI in combination with chemotherapy NSQ histology. The first 15 months of the Kaplan Meier line for pembrolizumab were plot digitized and fitted with an exponential curve to determine the monthly transition probability. The monthly probability was transformed into a weekly probability in TreeAge using the 'probtoprob' function. The monthly transition probability for ICI in combination with chemotherapy OS NSQ was 0.030.

The transition probability is based on the Kaplan Meier curve for the study population irrespective of PD-L1 status. Although the rate of death appears to decrease as PD-L1 expression increases, the clinical advice recommendation at the time of analysis was that if an ICI for use in combination therapy was funded in the first line, no PD-L1 expression would be required to access the treatment. The trial

data concerning the study population as a whole was therefore considered most relevant to inform the transition probability for an ICI in combination with chemotherapy.

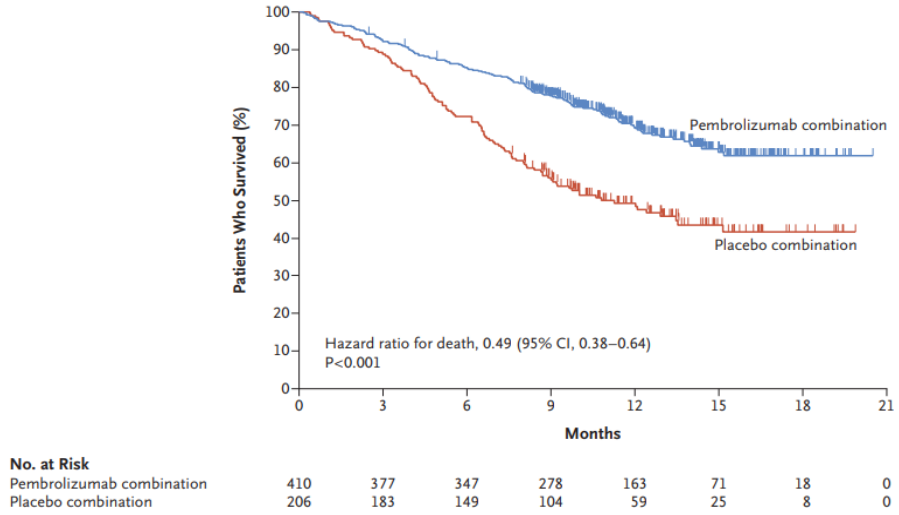

Figure 10 Kaplan-Meier OS curve (ITT population) KEYNOTE-189

First line ICI in combination with chemotherapy (SQ) – probability of progression and death (intervention arm only)

At the time of analysis, pembrolizumab was the only ICI agent with a positive clinical advice recommendation for use as a first line therapy in combination with chemotherapy. The transition probabilities in the model relating to the ICI in combination with chemotherapy with SQ histology first line was therefore derived from pivotal trial for pembrolizumab in this setting, KEYNOTE-407.

Figure 11 shows the PFS curve from KEYNOTE-407 that was used to determine the transition probability for first line ICI in combination with chemotherapy with SQ histology. The first 12 months of the Kaplan Meier line for pembrolizumab combination were plot digitized and fitted with an exponential curve to determine the monthly transition probability. The monthly probability was transformed into a weekly probability in TreeAge using the 'probtoprob' function. The monthly transition probability for ICI in combination with chemotherapy PFS SQ was 0.092.

Figure 12 shows the OS curve from KEYNOTE-407 that was used to determine the transition probability for first line ICI in combination with chemotherapy with SQ histology. The first 15 months of the Kaplan Meier line for pembrolizumab combination were plot digitized and fitted with an exponential curve to determine the monthly transition probability. The monthly probability was transformed into a weekly probability in TreeAge using the 'probtoprob' function. The monthly transition probability for ICI in combination with chemotherapy OS SQ was 0.035.

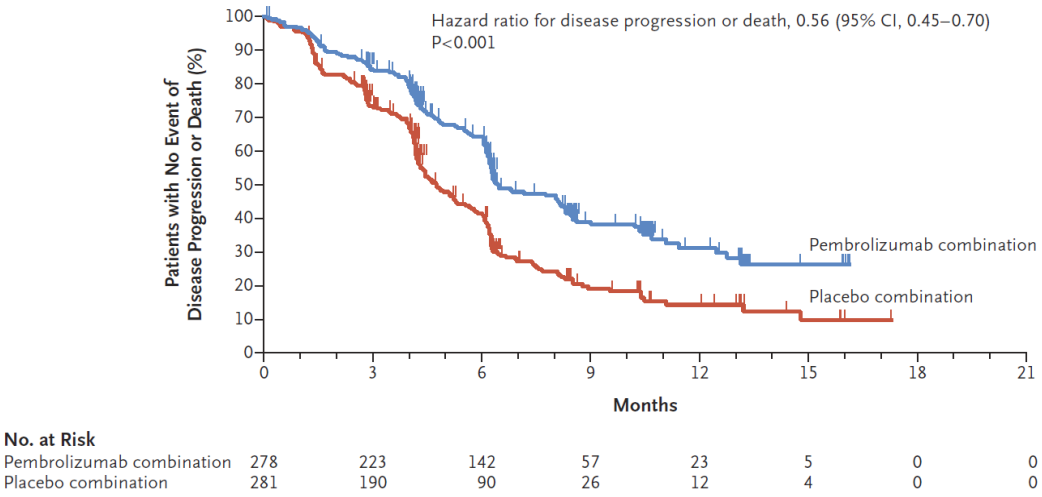

Figure 11 Kaplan-Meier PFS curve (ITT population) KEYNOTE-407

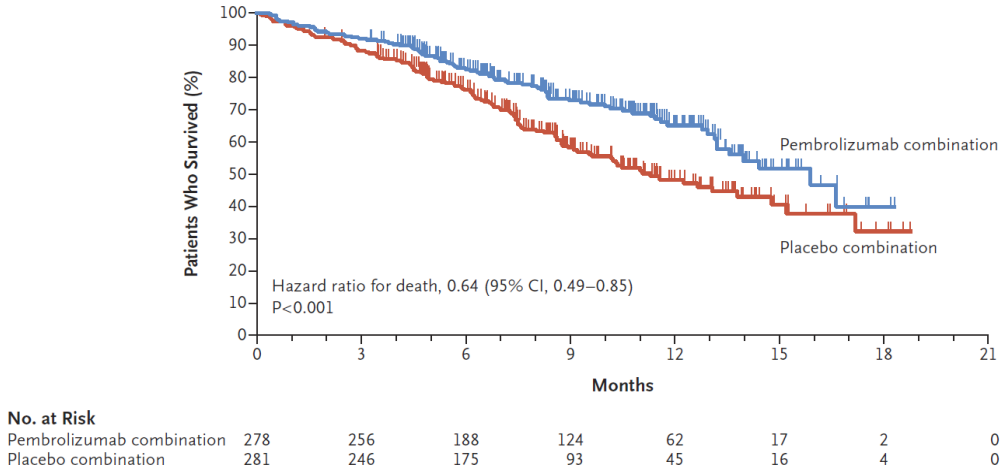

Figure 12 Kaplan-Meier OS curve (ITT population) KEYNOTE-407

NSQ chemotherapy - probability of progression and death (intervention and comparator arm)

The key transition probabilities for NSQ chemotherapy were derived from the Kaplan Meier curves in Figure 9 (PFS) and Figure 10 (OS) from KEYNOTE-189. Although the evidence from KEYNOTE-189 reflects the clinical efficacy of first line use, it was viewed as a conservative assumption to apply this to second line use in the intervention arm of the model. This was in part due to it being the best available evidence.

The PFS and OS Kaplan Meier line for pembrolizumab combination was plot digitised, plotted, and fitted with an exponential curve to determine the monthly probability. The first 14 and 15 months of the PFS and OS curves were plotted, respectively. The resulting monthly transition probability was 0.138 for NSQ chemotherapy PFS and 0.058 for NSQ chemotherapy OS.

The probability of progression was applied to both the intervention and comparator arm of the model in the NSQ chemotherapy health states. In the intervention arm of the model, the probability of death from NSQ chemotherapy is the same as the probability of death from ICI monotherapy (as the OS data is inclusive of patients who subsequently received chemotherapy). In the comparator arm of the model, the probability of death from NSQ chemotherapy is the probability of death calculated from KEYNOTE-189 as described above.

SQ chemotherapy – probability of progression and death (intervention and comparator arm)

The transition probabilities for SQ chemotherapy were derived from the Kaplan Meier curves in Figure 11(PFS) and Figure 12 (OS) from KEYNOTE-407. The PFS and OS Kaplan Meier line for pembrolizumab combination was plot digitised, plotted, and fitted with an exponential curve to determine the monthly probability. The first 12 and 15 months of the PFS and OS curves were plotted, respectively. The resulting monthly transition probability was 0.153 for SQ chemotherapy PFS and 0.056 for NSQ chemotherapy OS.

The probability of progression was applied to both the intervention and comparator arm of the model in the SQ chemotherapy health states. In the intervention arm of the model, the probability of death from SQ chemotherapy is the same is the probability of death from ICI monotherapy (as the OS data is inclusive of patients who subsequently received chemotherapy). In the comparator arm of the model, the probability of death from NSQ chemotherapy is the probability of death calculated from KEYNOTE-407 as described above.

Docetaxel – probability of progression and death (intervention and comparator arm)
The probability of progression from docetaxel in both arms of the model is derived from data in the comparator arm of trials 2L trials that compared ICI monotherapy in the 2L to docetaxel. The method of determining this probability is outlined below in the section titled “Docetaxel chemotherapy (intervention arm) - probability of progression and death”

BSC – probability of progression and death (intervention and comparator arm)

In both the intervention and comparator arm of the model the probability of progression while in BSC was calculated by multiplying the probability of progression on docetaxel by 1.56. This multiple reflects the ratio between the time to progression on docetaxel (2.5 months) and BSC (1.6 months) from Shepherd et al 2000.

In the intervention arm of the model, the probability of death in the BSC health state is a weighted probability between the probability of death from ICI monotherapy and ICI + chemotherapy. The probability is weighted by the proportion of people who start the model by taking an ICI as a monotherapy or in combination with chemotherapy and also by the proportion of NSQ and SQ histology within the ICI in combination with chemotherapy.

In the comparator arm of the model, the probability of death in BSC is a weighted probability of the probability of death in the NSQ and SQ chemotherapy arms with the weighting according to histology proportions.

Progressed disease – probability of death (intervention and comparator arm)
The probability of death in the progressed disease health state is the same as the probability of deaths described in the BSC health state above.

Table 12: Summary of 1L model transition probabilities

Health State	Monthly PFS Probability	Monthly OS probability	Source of data/Assumption
Intervention arm			
1L ICI monotherapy	0.094 0-5months 0.059 5+ months	0.029	KEYNOTE-024
1L ICI combination NSQ	0.079	0.030	KEYNOTE-189
1L ICI combination SQ	0.092	0.035	KEYNOTE-407
NSQ chemotherapy	0.138	Weighted average of the three OS probabilities above depending on the model scenario run.	KEYNOTE-189
SQ chemotherapy	0.153		KEYNOTE-407
Docetaxel	0.142		Average of OAK, KEYNOTE-010, CheckMate 017 (SQ) and CheckMate 057 (NSQ)
Best Supportive Care	0.222		Shepherd et al 2000
Progressed Disease	n/a		n/a
Comparator arm			
NSQ chemotherapy	0.138	0.058	KEYNOTE-189
SQ chemotherapy	0.153	0.056	KEYNOTE-407
Docetaxel	0.142	Weighted average of OS for SQ and NSQ chemotherapy 0.056	Average of OAK, KEYNOTE-010, CheckMate 017 (SQ) and CheckMate 057 (NSQ)
Best Supportive Care	0.222		Shepherd et al 2000
Progressed Disease	n/a		n/a

Second line model (by health state)

Intervention arm

ICI monotherapy – probability of progression and death

At the time of analysis, Pharmac had a positive clinical advice recommendation for the use of atezolizumab, nivolumab and pembrolizumab as a monotherapy in the second line setting. Furthermore, clinical advice from PTAC and CaTSoP (summarised in the clinical advice section of this TAR) considered that there was a class-effect among these agents in this setting. To determine the transition probability for PFS and OS for ICI monotherapy class as a second line agent, the Kaplan Meier curves of all three agents were plot digitised and fitted with an exponential to determine the monthly probability. In the case of Nivolumab where the trial data was available for each histology separately rather than combined, a probability for each histology was created and then a weighted average using the histology prevalence was calculated (75% NSQ, 25% SQ). The monthly transition probabilities from each agent where then averaged to determine the monthly transition probabilities for second line ICI monotherapy as a class. The resulting transition probabilities were converted to weekly transition probabilities in the TreeAge model using the 'probtoprob' function.

PFS

Figure 17 to Figure 20 below displays the Kaplan Meier PFS curves for the ICI being considered for use in a second line setting. The first 18 months, 15 months, 18 months and 20 months of the data was

plot digested for atezolizumab, nivolumab SQ, nivolumab NSQ and pembrolizumab respectively. The resulting monthly transition probability of PFS for each agent and for the class is displayed in Table 13.

OS

Figure 13 to Figure 16 below displays the Kaplan Meier OS curves for the ICI being considered for use in a second line setting. The first 24 months, 18 months, 21 months and 20 months of the data was plot digested for atezolizumab, nivolumab SQ, nivolumab NSQ and pembrolizumab respectively. The resulting monthly transition probability of OS for each agent and for the class is displayed in Table 13.

Table 13: Monthly Transition Probabilities for 2L ICI monotherapy PFS and OS

ICI therapy	Monthly probability of PFS	Monthly probability of OS	Data source
Atezolizumab	0.172	0.050	OAK trial
Nivolumab	0.117	0.057	CheckMate-017 /CheckMate-057
Pembrolizumab (2mg/kg)	0.056	0.055	KEYNOTE-010
Pembrolizumab (10mg/kg)	0.048	0.047	KEYNOTE-010
2L ICI monotherapy (average)	0.115	0.054	Average

Docetaxel chemotherapy (intervention arm) - probability of progression and death

The same method of calculation that was described in the section 'PFS and OS for 2L ICI monotherapy' above was used to determine the transition probabilities of docetaxel. The results of these calculations are displayed in Table 14 below. The transition probabilities calculated for docetaxel were used to inform the transition probabilities for docetaxel when it is used as a second line agent and third line agent in both the 1L and 2L models. This assumption was made as the trial data of docetaxel in the second line setting likely reflects the best estimate of efficacy in the third line setting and was considered a conservative assumption. The impact of this assumption is tested in the sensitivity analyses.

Table 14: Monthly Transition Probabilities for 2L Docetaxel PFS and OS

ICI therapy	Monthly probability of PFS	Monthly probability of OS	Data source
Docetaxel - Atezolizumab	0.138	0.068	OAK trial
Docetaxel - Nivolumab	0.208	0.087	CheckMate-017 /CheckMate-057
Docetaxel - Pembrolizumab (2mg/kg)	0.081	0.081	KEYNOTE-010
Docetaxel - Pembrolizumab (10mg/kg)	0.081	0.000	KEYNOTE-010
Docetaxel 2L (average)	0.142	0.078	Average

BSC (intervention) – probability of progression and death

In the intervention arm of the model the probability of progression while in BSC was calculated by multiplying the probability of progression on docetaxel by 1.56. This multiplier reflects the ratio between the time to progression on docetaxel (2.5 months) and BSC (1.6 months) from Shepherd et al 2000.

In the intervention arm of the model, the probability of death in the BSC health state is the same probability of death from ICI 2nd line monotherapy described above. The overall survival observed in the ICI monotherapy trials is assumed to be representative of the overall survival experience of the model population who like in the trial received subseuqnet lines of therapy.

Progressed disease (intervention) - probability of progression and death

In the intervention arm of the model, the probability of death in the progressed disease health state is the same probability of death from ICI 2nd line monotherapy described above. The overall survival observed in the ICI monotherapy trials is assumed to be representative of the overall survival experience of the model population who like in the trial received subseuqnet lines of therapy.

Comparator arm

The clinical trial evidence for the use of an ICI in a second line setting is compared to docetaxel. Not all patients are fit enough to take docetaxel so the comparator arm of this model separates out the experience of those patients who can have docetaxel and those who cannot by having a progress free and progressed disease health state for each group. In the intervention arm of this 2L model and both arms of the 1L model, a BSC health state exists to represent the PFS experience of those who can not have docetaxel. As described above, the probability of death is not different for those who can or cannot have docetaxel in other arms of the models as the OS data for these patient groups includes patients who can and those who cannot have docetaxel. This is not the case with the comparator arm of 2L trial data, hence the need for this different model structure.

PFS1: docetaxel

The probability of progression and death from docetaxel in the comparator arm of the 2L model is the same as the probability of progression and death from docetaxel described above in the section titled "Docetaxel chemotherapy (intervention arm) - probability of progression and death"

Progressed disease 1: docetaxel

The probability of death from docetaxel in the comparator arm of the 2L model is the same as the probability of death from docetaxel described above in the section titled "Docetaxel chemotherapy (intervention arm) - probability of progression and death"

PFS2: Best supportive care

In the comparator arm of the 2L model the probability of progression while in BSC was calculated by multiplying the probability of progression on docetaxel by 1.56. This multiple reflects the ratio between the time to progression on docetaxel (2.5 months) and BSC (1.6 months) from Shepherd et al 2000.

In the comparator arm of the 2L model the probability of death while in BSC was calculated by multiplying the probability of death on docetaxel by 1.63. This multiple reflects the ratio between the median overall survival on docetaxel (7.5 months) and BSC (4.6 months) from Shepherd et al 2000.

Progressed disease 2: Best supportive care

The probability of death from progressed disease following best supportive care is the same as the probability of death from PFS2: best supportive care, described above.

Table 15: Summary of 2L model transition probabilities

Health State	Monthly PFS Probability	Monthly OS probability	Source of data/Assumption
Intervention arm			
ICI monotherapy	0.142	0.054	Average of OAK, KEYNOTE-010, CheckMate 017 (SQ) and CheckMate 057 (NSQ)
Docetaxel	0.142		
Best Supportive Care	0.222		Shepherd et al 2000
Progressed Disease	n/a		
Comparator arm			
PFS1: Docetaxel	0.142	0.078	Average of OAK, KEYNOTE-010, CheckMate 017 (SQ) and CheckMate 057 (NSQ)
PD1: Docetaxel	n/a		
PFS2:BSC	0.222	0.127	Shepherd et al 2000
PD1: BSC	n/a		
Progressed Disease	n/a		n/a

Treatment duration and waning of treatment benefit

The base-case analysis considers a maximum treatment duration with an ICI of 2-years. This aligns with advice received from CaTSoP as well as what is recommended internationally. A sensitivity analysis with no treatment duration cap will be conducted.

The base-case analysis does not consider any waning of treatment benefit. The extrapolation of benefit beyond the horizon of clinical evidence, particularly for overall survival is a noted area of uncertainty internationally. In alignment with other international funding bodies, a sensitivity analysis was conducted to investigate the impact of waning of treatment benefit. In this scenario, the probability of death in the intervention arm is changed to the probability of death in the comparator arm after 5-years in the model.

Adverse events

No adverse events were considered as part of the base-case analysis. Sensitivity analyses were conducted to consider the effect of adverse events from a cost perspective.

Probability of starting the model in ICI monotherapy vs ICI with chemotherapy

In the intervention arm of the 1L model there is a variable which allows the proportion of the model cohort who receive ICI monotherapy compared to ICI in combination with chemotherapy.

When the scenario being run in the model requires ICI monotherapy and ICI with chemotherapy to be operate simultaneously, the proportion of patients who are assumed to be eligible for monotherapy ICI treatment depends on whether a PD-1 test is specified in the proposed special authority criteria.

If the funding scenario being considered permits both ICI monotherapy and ICI in combination with chemotherapy, and the proposed Special Authority criteria for monotherapy use does specify the need of a PD-1 test, the number of people assumed to have ICI monotherapy is 32%. This is the proportion

of patients in KEYNOTE189 who had a PD-L1 expression of greater than 50%. It is assumed that all patients who have a PD-L1 expression of greater than 50% would want to have monotherapy. Data from KEYNOTE-023, KEYNOTE-189 and KEYNOTE-407 suggests that the greatest benefit of treatment with an ICI inhibitor patient who have high PD-L1 expression and receive monotherapy. This patient group can then have platinum-based chemotherapy following disease progression meaning funding an ICI adds a line of therapy.

If the funding scenario being considered permits both ICI monotherapy and ICI in combination with chemotherapy, and the proposed Special Authority criteria for monotherapy use does not specify the need for a PD-1 test, then the number of people assumed to have ICI monotherapy is 10%. Clinical advice sought from CaTSoP suggested that given the invasive nature of testing PD-L1 status, if there was not a requirement in the special authority to have a PD-L1 test, clinicians would likely only test those who are not fit enough to receive ICI in combination with chemotherapy. This proportion is therefore going to be less than 32%. The assumption of 10% is uncertain and the impact is evaluated in sensitivity analyses.

Figure 13 to Figure 16 to below displays the Kaplan Meier overall survival curves for the ICI being considered for use in a second line setting.

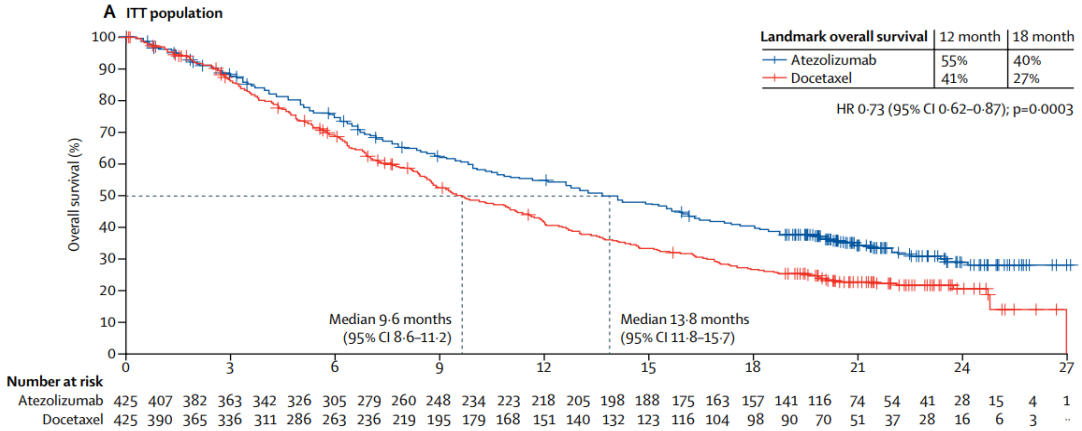

Figure 15: Kaplan-Meier OS curve Atezolizumab (ITT population) OAK trial

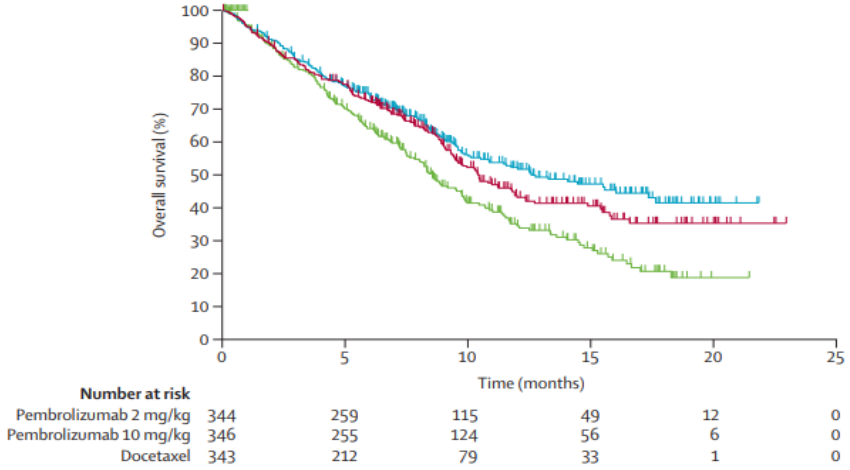

Figure 16 Kaplan-Meier OS curve Pembrolizumab KEYNOTE-010

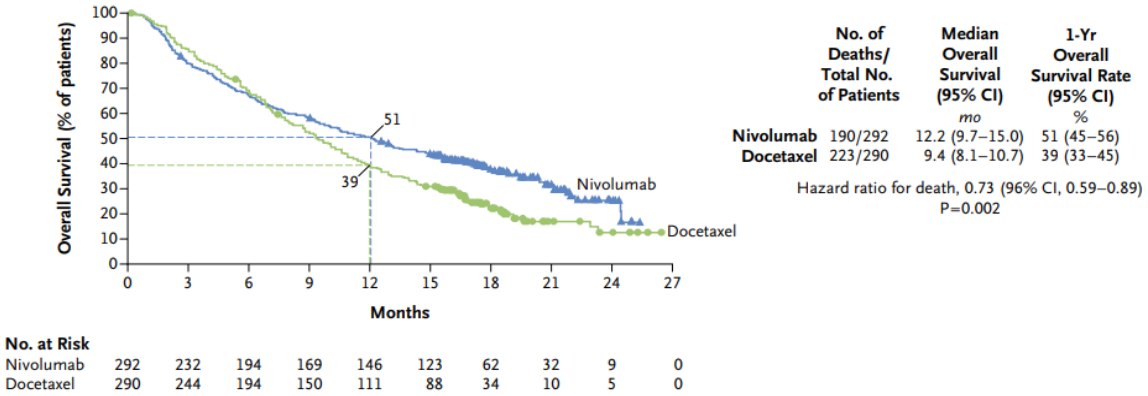

Figure 14: Kaplan-Meier OS curve Nivolumab NSQ – CheckMate-057

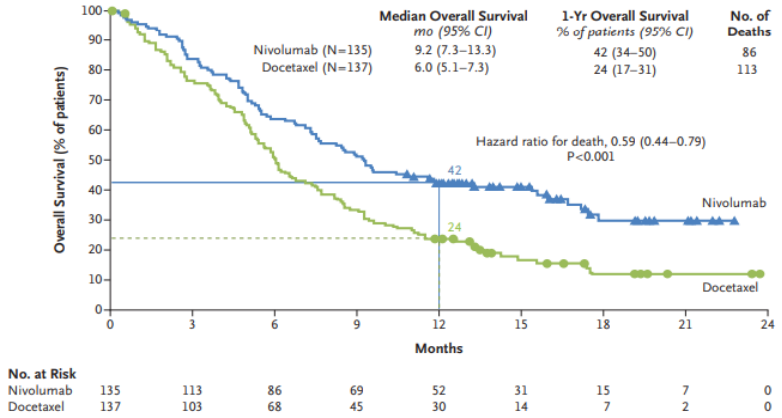

Figure 13 Kaplan-Meier OS curve Nivolumab SQ – CheckMate-017

Figure 17 to Figure 20 to below displays the Kaplan Meier PFS curves for the ICI being considered for use in a second line setting.

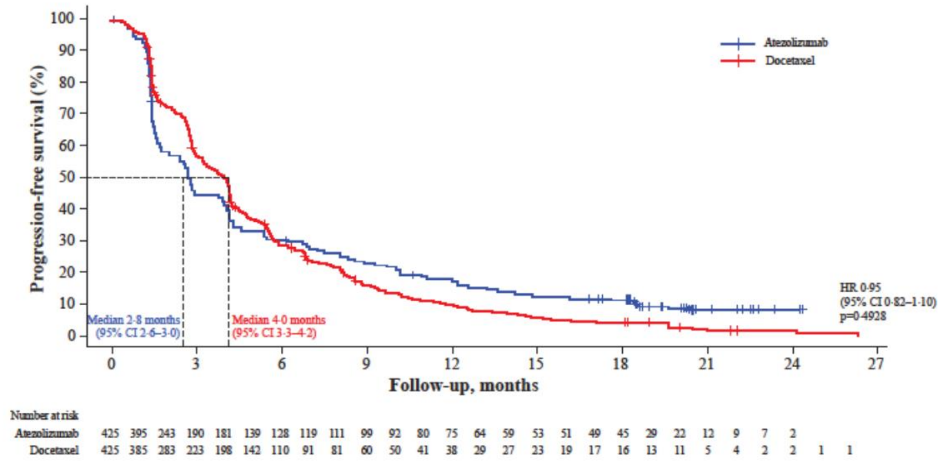

Figure 19: Kaplan-Meier PFS curve Atezolizumab (ITT population) OAK trial supplementary appendix

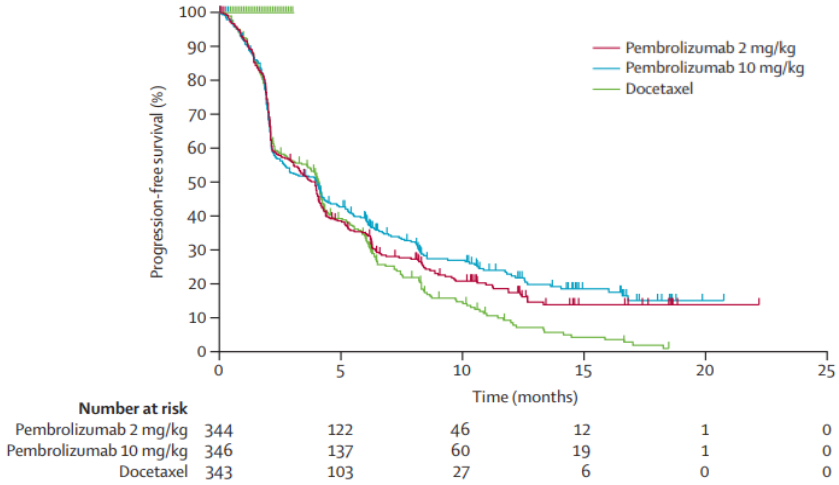

Figure 18 Kaplan-Meier PFS curve Pembrolizumab KEYNOTE-010

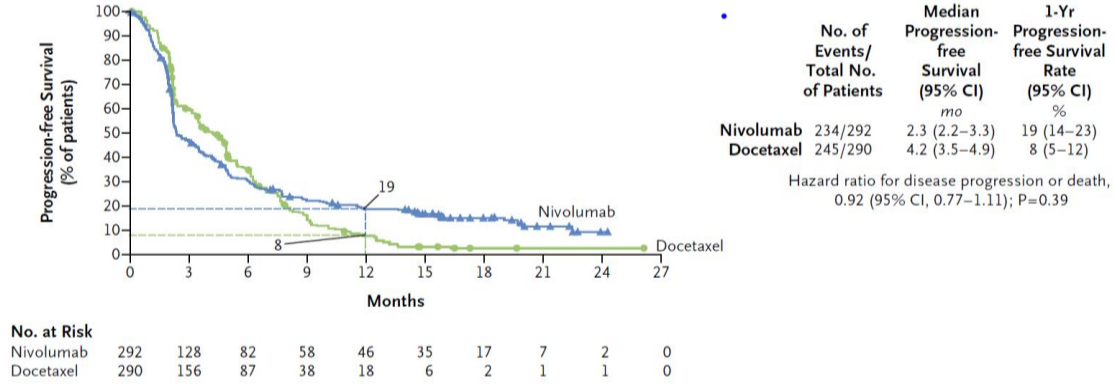

Figure 17: Kaplan-Meier PFS curve Nivolumab NSQ – CheckMate-057

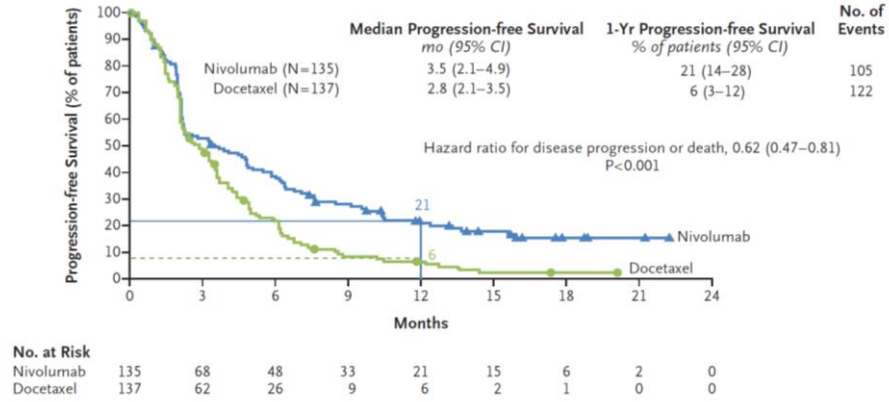

Figure 20 Kaplan-Meier PFS curve Nivolumab SQ – CheckMate-017

4.4 Health-Related Quality of Life

The health-related quality-of-life in the model was informed by Chouaid et al, 2013. The study looked at the health-related quality-of-life of patients with advanced NSCLC by assessing the quality of life of NSCLC patients in 25 hospitals across Europe. Health-related quality of life was measured in 390 patients using EurQOLs EQ-5D instrument. The resulting utilities by health state are shown in Figure 21.

Figure 21: Exert from Chouaid et al, 2013 displaying utility values by health state for NSCLC

TABLE 2. Calculated Utility Values and VAS Score by HS, PF, and PD

HS	Utility Values	Mean (SD); 95% CI	EQ-VAS Score	Mean (SD); 95% CI
All patients (N = 263)	255[a]	0.66 (0.29) [0.62–0.69]	257[b]	63.05 (20.89) [60.5–65.6]
HS1: first-line PF (n = 115)	111	0.71 (0.24) [0.67–0.76]	112	69.31 (18.33) [65.9–72.8]
HS2: first-line PD (n = 26)	26	0.67 (0.2) [0.59–0.75]	24	58.67 (17.4) [51.3–66.0]
HS3: second-line PF (n = 47)	44	0.74 (0.18) [0.68–0.80]	47	65.00 (19.6) [59.2–70.8]
HS4: second-line PD (n = 17)	17	0.59 (0.34) [0.42–0.77]	17	53.47 (23.25) [41.5–65.4]
HS5: third/fourth-line PF (n = 25)	24	0.62 (0.29) [0.49–0.74]	24	60.79 (21.5) [51.7–69.9]
HS6: third/fourth-line PD (n = 21)	21	0.46 (0.38) [0.28–0.63]	21	48.24 (21.86) [38.3–58.2]
HS7: BSC (n = 6)	6	NE[c]	6	NE[c]
PF (n = 190)	182[d]	0.70 (0.25) [0.66–0.73]	186[e]	66.64 (19.88) [63.8–69.5]
PD (n = 64)	64[f]	0.58 (0.32) [0.50–0.66]	62[g]	53.71 (20.80) [48.4–59.0]

[a]Sum of HS1–7 and six patients not classified to an HS. Eight patients had missing values on at least one of the EQ-5D questions, thus, a utility score was not calculated.
[b]Sum of HS1–7 and six patients not classified to an HS. Six patients had missing values to the VAS scale.
[c]Not evaluable. Patient sample was considered too small for a meaningful analysis.
[d]Sum of HS2, HS4, and HS6.
[e]Sum of HS1, HS3, HS5, and three patients in HS7.
[f]Sum of HS1, HS3, HS5, and three patients in HS7.
[g]Sum of HS2, HS4, and HS6.
VAS, Visual Analog Scale; PD, progressive disease; Ci, confidence interval; HS, health state; PF, progression-free; EQ, EuroQol; Qol, quality of life.

Given the cross over in the confidence intervals for the utility values between lines of treatment, the collective utility weight of 0.70 for PF and 0.58 for PD was modelled for both the first line and second line models. Sensitivity analysis around this were conducted.

The utility values chosen in the model broadly align with utility values determined in the relevant clinical trials and used as part of the supplier/applicant models described in Figure 21 various utilities summarised in Paracha et al, 2018, systematic review of health state utilities for metastatic NSLCC which focused on previously treated patients.

4.5 Costs

4.5.1 Pharmaceutical Cost

ICI monotherapy

The cost of each ICI therapy as a monotherapy is outlined below. Each treatment is indicated to be taken until disease progression, death or unacceptable toxicity.

Atezolizumab

Atezolizumab has three dosing regimens registered with MedSafe: 840mg every 2 weeks, 1200mg every 3 weeks and 1680 mg every 4 weeks. The most recent commercial offer Pharmac has received for Atezolizumab is a gross price per 1200mg vial of $9,503 and a confidential net price of S 9(2)(b)(ii), or S 9(2) per mg (A1361252). Table 16 below outlines the cost per dose for the three indicated dosage regimens.

Table 16: Net pharmaceutical cost of atezolizumab

Dose	Dose freq.	Cost per dose
840mg	2 weekly	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
1200mg	3 weekly	
1680mg	4 weekly	

Nivolumab

Nivolumab has three dosing regimens registered with Medsafe: 3mg/kg every 2 weeks, 240mg every two weeks, 480mg every 4 weeks. At the time of analysis, Pharmac listed nivolumab on the pharmaceutical schedule for melanoma. The gross price of the 40mg and 100mg vial respectively was $1051.98 and $2,629.96. The confidential net price of the 40mg and 100mg respectively was S 9(2)(b) and S 9(2)(b)(ii), (A901169). The net price per mg for both formulations is S 9(2)(b). Table 17 below outlines the cost per dose for the three indicated dosing regimens.

Table 17: Net pharmaceutical cost of nivolumab

Dose	Dose freq.	Cost per dose
3mg/kg	2 weekly	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
240mg	2 weekly	
480mg	4 weekly	

Pembrolizumab

There are two dosing regimens indicated for first line treatment (200mg 3 weekly and 400mg 6 weekly) and three for second line treatment (200mg 3 weekly, 400mg 6 weekly and 2mg/kg). At the time of analysis, Pharmac listed pembrolizumab on the pharmaceutical schedule for melanoma. The listed gross price for the 100mg vial is $4,680 and the confidential net cost after rebate is S 9(2)(b)(ii), (A920290). The price per mg is S 9(2)(b). Table 18 below outlines the cost per dose for the three indicated dosing regimens.

Table 18: Net pharmaceutical cost of pembrolizumab

Dose	Dose freq.	Cost per dose
200mg	3 weekly	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
400mg	6 weekly	
2mg/kg	3 weekly	

Chemotherapies

Table 19 below outlines the cost per dose of the various chemotherapy agents used in the model. Costs are as listed on the pharmaceutical schedule at the time of analysis. The various chemotherapy regimens including in the model are specified in detail below.

Table 19: Pharmaceutical price of chemotherapies

Agent	ECP price per mg (Pharmaceutical schedule)	Dose	Dose freq.	Cost per dose	Source of dose infomation
Carboplatin	$0.10	5 AUC	3 weekly	$57.50	EViQ Non Squamous histology
	$0.10	6 AUC	3 weekly	$69.00	EViQ SQ histology
Cisplatin	$0.25	75 mg/m2	3 weekly	$36.00	EviQ
Paclitaxel	$0.20	200 mg/m2	3 weekly	$76.80	EViQ
Pemetrexed	$0.55	500 mg/m2	3 weekly	$528.00	SA1679, Pharmaceutical Schedule
Docetaxel	$0.65	75 mg/m2	3 weekly	$93.60	EviQ

Squamous histology

The chemotherapy regimen modelled for squamous histology was carboplatin 200mg/m^2 and paclitaxel 6 AUC every 3 weeks for 4-6 cycles. This treatment regimen was the one permitted in KEYNOTE-407 and is believed to be the most common regimen for this patient population. KEYNOTE-407 also permitted the use of nab-paclitaxel in place of paclitaxel but at the time of analysis nab-paclitaxel was not listed in the Pharmaceutical schedule.

Table 20: Pharmaceutical cost of chemotherapy for squamous histology

Agent	Dose	Cost per dose	Cost per regimen
Paclitaxel	200mg/m2	$76.80	$145.80
Carboplatin	6 AUC	$69.00	

Non-squamous histology

Two chemotherapy regimens were included in the model for NSQ histologies. The two regimens were used in KEYNOTE-189 and are understood to be the most common regimen for this patient population (CaTSoP April 2019). The regimens comprise of either carboplatin (5 AUC) or cisplatin (75mg/m^2) in combination with pemetrexed (500mg/m^2). The two agents are taken together for 6 cycles after which only the pemetrexed component is continued on a 3-weekly basis until disease progression or unacceptable toxicity. The proportion of patients taking each regimen was weighted by the percentage of people on either regimen in KEYNOTE189 (72% carboplatin and 28% cisplatin).

Table 21: Pharmaceutical cost of chemotherapy for non-squamous histology

Regimen	Agent	Dose	Cost per dose	Cost per regimen
Carboplatin + pemetrexed	Pemetrexed	500mg/m2	$528.00	$585.50
	Carboplatin	5 AUC	$57.50	
Cisplatin + pemetrexed	Pemetrexed	500mg/m2	$528.00	$564.00
	Cisplatin	75mg/m2	$36.00	

4.5.2 Health Sector Costs

Administration costs

Table 22 below outlines the administration cost associated with all modelled treatments that are infusions. The costs are based on an hourly bed and nurse rate of $65 and $55 respectively and a one-off cost per infusion of specialist time of $35 (Cost Resource Manual). A one-off cost per infusion for compounding of $18 (15mins of a pharmacist's time) is included in the model (note: not included in Table 22 below). The infusion duration for the ICI was sourced from the agents respective MedSafe data sheets while infusion administration information on the remaining agents was sourced from EviQ, an Australian based, Local Government website which provides detailed treatment protocols that are representative of real-world use.

Table 22: Administration cost of all modelled treatment regimens

Regimen	Length of infusion	Cost per infusion	Source of administration time
ICI monotherapy	1 hour	$155	MedSafe data sheets
Carboplatin + paclitaxel	5 hours	$635	EviQ
Carboplatin + paclitaxel + pembrolizumab	6 hours for 4-6 chemo cycles 60mins thereafter	$755 $155	EviQ
Carboplatin + pemetrexed	2 hours 30 mins for pemetrexed maintenance	$275 $95	EviQ,
Carboplatin + pemetrexed + pembrolizumab	3 hours first 4-6 chemo cycles 2 hrs per subsequent cycle	$395 $275	EviQ, EviQ
Cisplatin + pemetrexed	4 hours	$515	EviQ
Cisplatin + pemetrexed + pembrolizumab	4 hours for first 4-6 chemo cycles 2 hours subsequent cycles	$635 $275	EviQ, EviQ
Docetaxel	1.5 hours	$215	EviQ

Monitoring costs

The cost of a seeing an oncologist ($362) and having a chest CT ($769) was included in the model every 12 weeks for all health states where patients are receiving treatment. (Cost Resource Manual)

PD-L1 testing

The cost of a PD-L1 test was modelled to be $200 per test.

When modelling scenarios that required PD-L1 testing an average cost of $625 was included at the start of the model for those patients in the monotherapy arm of the model. This average considers that approx. 900 first line patients will be tested but only 32% will test positive.

Other health sector costs

No adverse event costs were considered in the base-case as they were considered immaterial to the total costs incurred in the model. Sensitivity analyses were conducted to investigate the effect of adverse event costs.

4.6 Cost-Effectiveness Results and Sensitivity analyses by scenario

Proposal A – ICI funded for 1L monotherapy for patents with PD-L1 >50% only

The cost-utility of funding an ICI as 1L monotherapy for patients with a PD-L1 expression of greater than 50% (Proposal A - Figure 2) was evaluated using the first line model described above. The special authority for the patient population being considered is outlined in Section 2.2 above. The average cost of PD-L1 testing was included in this analysis as described in the special authority.

Table 23 below summarises the cost-effectiveness for funding either dosing regimen of atezolizumab or pembrolizumab if it were to be funded for metastatic NSCLC patients with a PD-L1 expression of greater than 50%. To date, Pharmac has not had a positive clinical advice recommendation for other ICI agents for Proposal A.

Table 23: Cost-effectiveness results of Proposal A by ICI agent

ICI	Incremental costs	Incremental QALY	Cost per QALY	QALYs per $million
Atezolizumab 1200mg 3 weekly	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	0.83	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
Atezolizumab 1680mg 4 weekly		0.83		
Pembrolizumab 200mg 3 weekly		0.83		
Pembrolizumab 400mg 6 weekly		0.83		

Table 24 below summaries the key sensitivity analyses conducted for proposal A assuming the ICI being considered is atezolizumab 1200mg. At the time of analysis, S 9(2)(b)(ii), 9(2) represented the most cost-effective option for funding an ICI for Proposal A. This will need to be re-assessed following receipt of new commercial proposals.

Base-case cost-effectiveness: S 9 QALYs per million dollars spent

Likely cost-effectiveness range: S 9(2) QALYs per million dollars spent

The model is most sensitive to the changes in the cost of the ICI and overall survival. The likely range presented represents the CUA results if overall survival values and associated hazard ratios from KEYNOTE024's long-term follow-up data (which included adjustments for trial cross-over) were used in the model. Likely variation in disease monitoring costs, utilities, and progression-free survival are incorporated in this CUA range.

Table 24: Summary of key sensitivity analysis conducted for proposal A

Scenario	QALYs per $million
Base-case S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
No 2-year treatment max	
Incremental utility gain halved	
Incremental utility gain doubled	
25% price reduction in ICI agent+	
Adverse events - 10% of people will incur a one of adverse requiring $15,000 of treatment (added to model incremental cost)	
Adverse events -5% of people on ICI treatment receive $1000 weekly cost	
Cost of disease monitoring doubled	
Treatment effect stopped at 5-years	

Probability PFS on ICI treatment 10% greater than comparator chemotherapy	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
Probability PFS on ICI treatment 10% lower than comparator chemotherapy	
OS from KEYNOTE 024 trial - chemotherapy (0.49)	
OS KEYNOTE 024 trial - chemotherapy lower confidence interval	
OS from KEYNOTE 024 trial - chemotherapy ITT hazard ratio	
[+] Sensitivity analysis on the price of an ICI are indicative only and are not considered in the likely cost-effectiveness estimate.	

Proposal B – ICI funded for second line use only

The cost-utility of funding an ICI for 2L (Proposal B - Figure 2) was evaluated using the second line model described above. The special authority for the patient population being considered is outlined in Section 2.2 above.

Key assumptions in this model were 50% of people who progressed to 3L therapy in the intervention arm had docetaxel while the remaining 50% had best supportive care. In the base-case there was a 2-year maximum treatment duration with an ICI.

Table 25 below summaries the cost-effectiveness of funding an ICI for Proposal B by ICI and dosing regimen.

Table 25: Cost-effectiveness results of Proposal B by ICI agent

ICI and dose	Incremental costs	Incremental QALY	Cost per QALY	QALY per $million
Atezolizumab 1200mg 3 weekly	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	0.41	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
Atezolizumab 1680mg 4 weekly		0.41		
Nivolumab Fixed Dose (240mg 4 weekly)		0.41		
Nivolumab weight-based dosing (3mg/kg 2 weekly)		0.41		
Pembrolizumab 200mg 3 weekly		0.41		
Pembrolizumab 400mg 6 weekly		0.41		

Table 26 below summaries the key sensitivity analyses conducted for proposal B assuming the ICI being considered is S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j). At the time of analysis, S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) represented the most cost-effective option for funding an ICI for Proposal B.

Base-case cost-effectiveness S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j): S 9(2)(j) QALYs per million dollars spent

Likely cost-effectiveness range S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j): S 9(2)(b)(ii), 9(2)(j) QALYs per million dollars spent

The cost of ICI in the model is based on S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) as this represents the most cost-effective price at the time of analysis. The model is sensitive to the cost of the ICI and overall survival. The likely range represents the cost-effectiveness if the incremental difference in OS in base-case was varied by +25% and -25%. This range incorporates uncertainty in the proportion of people using docetaxel, variation in the cost of disease monitoring, a scenario where there is no treatment duration max for ICI treatment, and a maximum 5-year treatment effect.

Table 26: Summary of key sensitivity analysis conducted for proposal B

Scenario description	QALY per $million
Base case: S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
Comparator arm - proportion receiving 2L docetaxel (0%)	
Comparator arm - proportion receiving 2L docetaxel (100%)	

Proportion receiving docetaxel 75% both arms	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
Proportion receiving docetaxel 25% both arms	
Treatment duration of ICI	
25% price reduction cost per mg of modelled ICI+	
50% price reduction cost per mg of modelled ICI+	
Adverse event - 10% of people will incur a one of adverse requiring $15,000 of treatment (added to incremental cost of the model)	
Adverse events - $1000 for 43% for PD-L treatment (intervention arm) and 15% of docetaxel (comparator arm only) (proportion as observed in the OAK trial)	
Cost of disease monitoring doubled	
Treatment effect stopped at 5-years.	
OS halved - applied to intervention arm	
OS -25% - applied to intervention arm	
OS +25% - applied to intervention arm	
OS doubled - applied to intervention arm	
PFS and OS values from OAK trial used instead of class average	
PFS and OS values from CHECKMATE trial used instead of class average	
+ Sensitivity analysis on the price of an ICI are indicative only and are not considered in the likely cost-effectiveness estimate.	

Proposal C – ICI funded for 1L use (monotherapy and combination therapy available)

The cost-utility of funding an ICI for 1L monotherapy and combination therapy (Proposal C- Figure 2) was evaluated using the first line model described above. The special authorities for the patient population being considered is outlined in Section 2.2 above.

Table 27**Table *27*:** Cost-effectiveness results of Proposal C by ICI agent below summaries the cost-effectiveness of various possible funding scenarios for funding an ICI for 1L use. The scenarios vary the ICI agent funded for combination or monotherapy use and whether or not a PD-L1 test would be required. As described in the modelling methods above, the proportion of patients who would take an ICI first line as a monotherapy or combination therapy would vary depending on whether evidence of a PD-L1 expression of >50% would be required to access monotherapy or not. As is evident in the table below, the impact of mandating PD-L1 testing in a special authority has minimal impact if the same ICI is listed for both monotherapy and combination therapy but can have a more significant impact if different agents are used.

Table 27: Cost-effectiveness results of Proposal C by ICI agent

Funding scenario	Incremental costs	Incremental QALY	Cost per QALY	QALY per $million
Monotherapy: atezolizumab** Combination: pembrolizumab*** (PD-1 testing - 32% receiving monotherapy)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	0.72	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
Monotherapy: atezolizumab** Combination: pembrolizumab*** (No PD-1 testing - 10% receiving monotherapy)		0.69		
Monotherapy: pembrolizumab*** Combination: pembrolizumab*** (PD-1 testing - 32% receiving monotherapy)		0.72		
Monotherapy: pembrolizumab*** Combination: pembrolizumab*** (No PD-1 testing - 10% receiving monotherapy)		0.69		
Monotherapy: atezolizumab** Combination: atezolizumab** (PD-1 testing - 32% receiving monotherapy)		0.72		
Monotherapy: atezolizumab** Combination: atezolizumab**		0.69		

(No PD-1 testing – 10% receiving monotherapy)				
*Note: at the time of writing the TAR there was no positive clinical advice recommendation to fund atezolizumab for combination therapy **Atezolizumab 1200mg 3 weekly *** Pembrolizumab 400mg 6 weekly				

1L monotherapy and 1L combination therapy – PD-L1 testing required

Table 28 below summaries the key sensitivity analysis conducted for the funding scenario were PD-L1 testing is required as part of the special authority. 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)

Table 28 Summary of key sensitivity analysis conducted for proposal C (PD-L1 testing required)

Scenario description	QALY per $million
Base-case: Monotherapy: S 9(2)(b)(ii), 9 ** Combination: S 9(2)(b)(ii), 9(2) *** (PD-1 testing - 32% receiving monotherapy	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
2-year treatment duration with ICI	
Difference in utility between PFS and PD halved (applied to PFS)	
Difference in utility between PFS and PD doubled (applied to PFS)	
25% price reduction in ICI+	
50% price reduction In ICI+	
Adverse events - assuming that 10% of people will incur a one of adverse requiring $15,000 of treatment (Added to incremental cost)	
Cost of disease monitoring doubled	
Treatment effect stopped at 5-years.	
OS 2019 KEYNOTE 024 trial - chemotherapy (0.49)	
OS 2019 KEYNOTE 024 trial - chemotherapy lower CI HR 0.34	
OS 2019 KEYNOTE 024 trial - chemotherapy ITT HR	
S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
+ Sensitivity analysis on the price of an ICI are indicative only and are not considered in the likely cost-effectiveness estimate.	

Base-case cost-effectiveness: S 9 QALYs per $1m.
Likely cost-effectiveness: S 9(2) QALYs per $1m.

The CUA results presented represent a funding scenario where the Special Authority will contain a requirement that a PD-L1 test showing an expression of greater than 50% will be required for patients to receive ICI monotherapy. All remaining patients are assumed to have ICI in combination with platinum-based chemotherapy. The model is 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). This represents the most cost-effective funding scenario at the point of analysis (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 model is most sensitive to variation in the price of the ICI inhibitors and overall survival. The likely range presented represents the CUA if overall survival values and associated hazard ratios from KEYNOTE024s long-term follow-up data (which included adjustments for trial cross-over) were used in the model.

1L monotherapy and 1L combination therapy – no PD-L1 testing required

Table 29 below summaries the key sensitivity analysis conducted for the funding scenario were no PD-L1 testing is required as part of the special authority, S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) This represents the most cost-effective funding scenario for proposal C for Pharmac at the time of analysis 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 29 Summary of key sensitivity analysis conducted for proposal C (no PD-L1 testing required)

Scenario description	QALY per $million
Base-case: Monotherapy S 9(2)(b)(ii), 9 ** Combination: S 9(2)(b)(ii), 9(2) *** (no PD-1 testing - 10% receiving monotherapy	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
2-year treatment duration of ICI	
Difference in utility between PFS and PD halved (applied to PFS)	
Difference in utility between PFS and PD doubled (applied to PFS)	
25% price reduction in ICI	
50% price reduction in ICI	
Adverse events - if 10% of people will incur a one of adverse requiring $15,000 of treatment	
Cost of disease monitoring doubled	
Treatment effect stopped at 5-years	
OS 2019 KEYNOTE 024 trial - chemotherapy (0.49)	
OS 2019 KEYNOTE 024 trial - chemotherapy lower CI HR 0.34	
OS 2019 KEYNOTE 024 trial - chemotherapy ITT HR	
**S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)	
+ Sensitivity analysis on the price of an ICI are indicative only and are not considered in the likely cost-effectiveness estimate.	

Base-case cost-effectiveness: S 9 QALYs per $1m.
Likely cost-effectiveness: S 9 QALYs per $1m.

The CUA results presented represent a funding scenario where the Special Authority will not contain a requirement to test for PDL1 expression. In this scenario, it is estimated that 10% of the 1L population will receive ICI monotherapy with S 9(2)(b)(ii), 9(2). All remaining patients are assumed to have S 9(2)(b)(ii), 9(2) in combination with platinum-based chemotherapy. This represents the most cost-effective funding scenario at the point of analysis (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 model is most sensitive to variation in the price of the ICI inhibitors and overall survival. The likely range presented represents the CUA if overall survival values and associated hazard ratios from KEYNOTE024s long-term follow-up data which included adjustments for trial cross-over were used in the model.

Note: The cost-effectiveness of first line combination therapy only was not considered. Clinical efficacy data and clincial advice received by Pharmac to date considers that the health benefit from ICI treatment is the greatest for those patients who have a high PD-L1 expression (>50%) and so it would not be reasonable to fund combination use without also funding monotherapy use.

Proposal D – ICI funded for first line use in patients with PD-L1>50% and in second line for those with PD-L1<50%.

Base-case cost-effectiveness: S 9(2) QALYs per $1m.

Likely cost-effectiveness: S 9(2) QALYs per $1m.

The CUA estimate is based on the funding of S 9(2)(b)(ii), 9(2) for 1L patients with a high PD-L1 expression and 2L patients with a low PD-L1 expression. This is a weighted CUA result with the CUA results from the two individuals weighted by population size as in the BIA below. The largest driver of uncertainty in both models is overall survival. The CUA ranges represent likely variation in overall survival and use the same scenarios as described in the individual models.

Proposal E – ICI funded for first line and second line use – one line of treatment permitted per patient.

Base-case cost-effectiveness: S 9 QALYs per $1m.

Likely cost-effectiveness: S 9(2) QALYs per $1m.

The CUA in this scenario (E) is estimated to be the same as the CUA of funding 1L only. There will be a small increase in the CUA of the listing in the first year due to the prevalent bolus of 2L patients but long term the CUA of this investment will represent the funding of the 1L only population.

The CUA results presented represent a funding scenario where the Special Authority will contain a requirement that a PD-L1 test showing an expression of greater than 50% will be required for patients to receive ICI monotherapy. All remaining patients are assumed to have ICI in combination with platinum-based chemotherapy. The model is 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). This represents the most cost-effective funding scenario at the point of analysis (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 model is most sensitive to variation in the price of the ICI inhibitors and overall survival. The likely range presented represents the CUA if overall survival values and associated hazard ratios from KEYNOTE024's long-term follow-up data (which included adjustments for trial cross-over) were used in the model.

5. Budget Impact Analysis

5.1 Patient Numbers

First line

Table 30 below outlines the calculation that was done to estimate the number of eligible patients in New Zealand who could receive first line therapy with an ICI if it were funded for metastatic NSCLC patients.

Table 30: Calculation of eligible first line metastatic NSCLC patients in New Zealand

Lung cancer incidence		2037	2013 Cancer Registry
Proportion with non-small cell lung cancer	85%	1731	https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html
Proportion with metastatic disease at diagnosis	48%	831	https://thorax.bmj.com/content/68/6/551
Proportion with non-metastatic disease at diagnosis	52%	900	
Proportion with non-metastatic disease at diagnosis who will progress to metastatic disease	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)		
Total		1209	
Proportion of NSCLC + Squamous	25%	302	https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html
Proportion of NSCLC + non-Squamous	75%	907	https://www.cancer.org/cancer/non-small-cell-lung-cancer/about/what-is-non-small-cell-lung-cancer.html
proportion of NSQ without EGFR+	70%	635	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5346692/
Total		937	

Second line

The estimated number of people who would likely receive an ICI second line if it was funded was estimated to be 800 people. This value was carried forward from a previous TAR (292) and is being re-evaluated.

5.2 Budget impact

The budget impact assessment was conducted in TreeAge using the same model assumptions described above except for the discount rate which was changed to 0% in order to get an undiscounted trace. The BIA was then discounted at 8% per annum. The BIA therefore is inclusive of subsequent treatment costs in both the intervention and status quo arms of the model if they occur in the 5-year budget impact time frame. The resulting model expenditure each year was then multiplied by the estimated patient numbers per year taking into account the number of new or prevalent patient per year.

Proposal A – ICI funded for 1L monotherapy for patents with PD-L1 >50% only

The BIA below for proposal A is based on 32% of the incident 1L population of 900 patients having a PD-L1 expression of greater than 50%. The BIA is based on the price of S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) as this represents the lowest cost ICI at the time of analysis. The health sector costs include the cost of PD-L1 testing for 900 people each year.

Table 31: Budget impact Assessment Proposal A

Year	1	2	3	4	5	5-year NPV
Incident patients	288	288	288	288	288	
Pharmaceutical costs (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Other health sector costs (million)	$0.31	$1.00	$1.39	$1.57	$1.66	$4.89
Total Health Sector Budget Impact (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

Proposal B – ICI funded for second line use only

The BIA below for Proposal B is based on 800 incident patients a year receiving S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j). Pharmaceutical costs consider the cost of S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) and docetaxel. Health sector costs included infusion services and disease monitoring.

Table 32: Budget impact Assessment Proposal B

Year	1	2	3	4	5	5-year NPV
Incident patients	800	800	800	800	800	
Pharmaceutical costs (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Other health sector costs (million)	$1.66	$2.23	$2.35	$2.38	$2.38	$9.38
Total Health Sector Budget Impact (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

Proposal C – ICI funded for 1L use (monotherapy and combination therapy available)

<u>With PD-L1 testing</u>

The BIA below is based on 32% of the incident 1L population of 900 patients having a PD-L1 expression of greater than 50% receiving 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 health sector costs include the cost of PD-L1 testing 900 people each year.

Table 33 Budget impact Assessment Proposal C – with PD-L1 testing

Year	1	2	3	4	5	5-year NPV
Incident patients	900	900	900	900	900	
Pharmaceutical costs (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Other health sector costs (million)	$0.43	$1.73	$2.44	$2.74	$2.89	$8.42
Total Health Sector Budget Impact (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

<u>No PD-L1 testing</u>

The BIA below is based on 10% of the incident 1L population of 900 patients having a PD-L1 expression of greater than 50% receiving 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 34: Budget impact Assessment Proposal C – no PD-L1 testing

Year	1	2	3	4	5	5-year NPV
Incident patients	900	900	900	900	900	
Pharmaceutical costs (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Other health sector costs (million)	$0.08	$1.10	$1.65	$1.87	$1.97	$5.45
Total Health Sector Budget Impact (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

Proposal D – ICI funded for first line use in patients with PD-L1>50% and in second line for those with PD-L1<50%.

The BIA below for Proposal D below represents a scenario where S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) is funded for patients in a 1L setting who have a PDL1 expression of greater than 50% and that all other patients will be able to receive an ICI in 2L. The patient numbers in the 1L setting are based on 32% of the 900 1L incident patients having a PD-L1 expression of greater than 50%. The patient numbers in the 2L are based on 68% of the 800 estimated 2L patients having a low PD-L1 expression. The cost of testing all 900 1L patients for PDL1 expression is included in the health sector costs. No prevalent bolus of patients in either line upon funding is considered.

Table 35 Budget impact Assessment Proposal D

Year	1	2	3	4	5	5-year NPV
Incident patients	288 1L 544 2L	288 1L 544 2L	288 1L 544 2L	288 1L 544 2L	288 1L 544 2L	
Pharmaceutical costs (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Other health sector costs (million)	$1.44	$2.52	$2.99	$3.18	$3.28	$11.27
Total Health Sector Budget Impact (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

Proposal E – ICI funded for first line and second line use – one line of treatment permitted per patient.

The BIA below for Proposal E represents a funding scenario where S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j) S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j). In this scenario, 32% of patients would be expected to have a PD-L1 expression of greater than 50% and receive montherapy 1L treatment. A prevalent bolus of 2L patients who would have treatment in the first year of the listing is considered. Beyond this point, all patients are assumed to receive an ICI in the 1L.

Table 36: Budget impact Assessment Proposal E

Year	1	2	3	4	5	5-year NPV
Incident patients	900 1L 800 2L	900 1L	900 1L	900 1L	900 1L	
Pharmaceutical costs (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Other health sector costs (million)	$2.09	$2.30	$2.56	$2.76	$2.89	$10.73
Total Health Sector Budget Impact (million)	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					