TAR 375 – Alectinib for anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer

This assessment provides an estimate of the likely cost-effectiveness range of alectinib for non-small cell lung cancer. Note that this is a rapid analysis - this estimate may need to be further validated with a more detailed cost-utility analysis.

Executive summary

In New Zealand, 2,100 people are diagnosed with late stage non-small cell lung cancer (NSCLC) each year. Treatment choice is informed by histology, specifically whether the cancer is squamous or non-squamous in origin. In the setting of non-squamous NSCLC, diagnostics have improved one step further, by identifying subcategories of oncogenes. This proposal looks at one such oncogene, called anaplastic lymphoma kinase (ALK), a receptor tyrosine kinase (RTK) that can become permanently switched on in some NSCLC patients leading to uncontrolled cell proliferation. PHARMAC staff estimate there are approximately 40 NSCLC patients in this ALK+ subgroup each year in New Zealand.

Alectinib is an oral ALK inhibitor. Evidence to date has examined the ability of alectinib to improve progression free survival, overall survival, and to decrease the rate of brain metastasis compared to patients managed on existing treatments.

Pharmacoeconomic analysis was undertaken in October 2018 by the health economics team to evaluate this proposal for prioritisation. This analysis has been updated in August 2019 to account for the updated pharmaceutical pricing offered by the Supplier. On average, patients are estimated to gain 2.22 QALYs for an incremental cost of S 9(2)(b)(ii), 9(2)(ba)(i) & (central estimate S 9(2) QALYs per $1m; cost per QALY of S 9(2)(b)), with likely cost effectiveness range between S 9(2)(b)(ii), QALYs per $1m, and possible range between S 9(2) S 9 ALYs per $1m. The likely range is informed by uncertainty in the annual number of NSCLC patient who will require ALK testing. The possible range is informed by uncertainty of the incremental quality of life benefit of patients managed on alectinib versus chemotherapy.

Overall, the five-year net impact to DHB budgets from listing alectinib is estimated to be S 9(2)(b) (NPV; 8% discount), with a cost of S 9(2)(b)(ii), in the first financial year. This assumes 23 patients receive treatment with alectinib in the first year increasing to 50 patients in outyears.

A summary of the proposal is provided in the table below.

PROPOSAL OVERVIEW
Pharmaceutical Alectinib (Alecensa) 150mg tablet
Supplier Roche Products (New Zealand) Ltd
Proposed Indication ALK-positive (ALK+) non-small cell lung cancer (NSCLC)
Dosing 600mg PO BD cc (four tablets taken orally, twice daily, with food)
Pharmaceutical Price $[redacted] per pack of 224x 150mg tablets. May 18th, 2018 (Supplier application)
PTAC PRIORITY Medium (PTAC August 2018)
PHARSIGHT REFERENCE https://pharsight.pharmac.govt.nz/bin/pharsight.php?Page=Proposal&ProposalId=1670&ProspectId=0

1. Proposal Overview

1.2 Summary

An application for the funding of alectinib (Alecensa) for the first-line treatment of anaplastic lymphoma kinase (*ALK*)-positive, locally-advanced or metastatic non-small cell lung cancer (NSCLC) was received from Roche Products (New Zealand) Ltd in May 2018.

The table below provides a summary of the patient population; intervention; comparator treatment; and main outcomes of treatment.

Table 1. PICO

PICO	
POPULATION	Patients with untreated non-small cell lung cancer with ALK mutation
INTERVENTION	Alectinib
COMPARISON	Platinum based chemotherapy
OUTCOME	Progression free survival, Overall survival

1.3 Patient Population

A detailed description of the patient population has been provided in the PTAC paper that accompanied this application to the August 2018 PTAC meeting. A summary of this information is provided below.

Disease description

Lung cancer refers to malignancies originating in the airways or pulmonary parenchyma. Approximately 95% of lung cancers can be categorised as either NSCLC or small cell lung cancer (SCLC). NSCLC is the most common type, accounting for approximately 75% of all cases. NSCLC can be further grouped into squamous (~30%) and non-squamous (~70%) carcinoma subtypes. Non-squamous NSCLC subtypes include adenocarcinoma, large-cell carcinoma, and undifferentiated carcinoma. Squamous NSCLC is considered a distinct disease that is characterized by an aggressive course and poor response to treatment.

Approximately 4-5% of patients with NSCLC have a chromosomal rearrangement of the *ALK* gene; the vast majority of which are reported in non-squamous NSCLC. These rearrangements lead to the expression of constitutively active ALK fusion proteins, which have downstream effects that include promoting tumour cell growth and survival. *ALK* gene rearrangements are generally mutually exclusive with *EGFR* and *KRAS* mutations.

ALK-positive NSCLC has a poorer prognosis than NSCLC associated with other oncogenic drivers. Patients generally have a more advanced stage of disease at diagnosis, have a high lifetime risk of central nervous system (CNS) metastases, and a high frequency of brain metastases at diagnosis.

Epidemiology

Lung cancer is the leading cause of cancer-related death in New Zealand each year, despite lung cancer being the fifth most commonly diagnosed cancer in New Zealand. In 2015, 2177 new cases of lung cancer were diagnosed in New Zealand, correlating to an incidence of 29 per 100,000 population.[1] Metastatic disease is diagnosed in 51% of NSCLC patients at presentation. *ALK* gene rearrangements are found in 4-5% of NSCLC patients. Using these assumptions, the supplier has estimated that approximately 40 patients per year will be identified as having *ALK*-positive NSCLC. In comparison, CaTSoP advised that between 40-70 patients would be eligible for treatment each year.

1.4 Current Treatment in New Zealand

Advanced lung cancer is considered incurable; the aim of treatment is to extend life expectancy and improve quality of life.

Standard first-line treatment for advanced NSCLC for patients in New Zealand is platinum-based chemotherapy in combination with pemetrexed (non-squamous) or gemcitabine or paclitaxel (squamous). Patients who progress on platinum-based chemotherapy and elect to have further treatment will additionally receive docetaxel. However, docetaxel has a considerable side effect profile which may influence individual patient decision to progress onto this therapy.

1.5 Intervention

Clinical Pharmacology and Mechanism of Action

The ALK gene is highly conserved, encoding a receptor tyrosine kinase (RTK) that belongs to the insulin-receptor superfamily. Under normal conditions, ligand binding induces RTK homodimerisation. Homodimerisation leads to trans-phosphorylation and kinase activation. Activating mutations or translocations of the ALK gene enable ligand-independent activation of the ALK encoded receptor, resulting in constitutive activation and uncontrolled cell proliferation.

Alectinib is a second-generation RTK-inhibitor that targets ALK and RET tyrosine kinase. Alectinib inhibits ALK tyrosine kinase activity, leading to inhibition of downstream signalling pathways including STAT3 and PI3K/AKT, and inhibits proliferation of cancer cells harbouring ALK fusion proteins.

An application for another ALK inhibitor, crizotinib, has also been considered by PTAC. Crizotinib is a first-generation ALK inhibitor that targets the c-MET, ALK, and ROS1 RTKs. Despite good initial responses to crizotinib, many patients develop resistance within a few years. Alectinib also has activity against mutant forms of the ALK enzyme responsible for resistance to crizotinib, and unlike crizotinib, is also able to penetrate the CNS.

[1] New Zealand Cancer Registry. Ministry of Health. Available at: https://www.health.govt.nz/publication/new-cancer-registrations-2015. (Accessed: 1st August 2019).

New Zealand Registration

Alectinib is registered for use in New Zealand for the treatment of adult patients with *ALK*-positive, locally advanced or metastatic NSCLC.

Patent information

Patent expiry is listed in the supplier application as June 9th, 2030.

Recommended Dosage

The recommended dose of alectinib is 600 mg (four 150 mg capsules) given orally, twice daily with food (total daily dose of 1200 mg). Treatment should be continued until disease progression or unacceptable toxicity.

No dose adjustment is required for elderly patients or patients with renal or mild hepatic impairment. Alectinib has not been studied in patients with moderate to severe hepatic impairment.

2. Health Benefits

2.1 Clinical Evidence

The supplier application contained the results of three trials providing evidence in support of the efficacy of alectinib for the treatment of *ALK*-positive NSCLC, as outlined below in Table 2. Of these, the results of the ALEX trial are the most relevant to the target population considered in this TAR (1-3).

Table 2. Clinical evidence reviewed by PTAC / CaTSoP.

Trial Name	Detail	Citation(s)
ALEX	Phase 3, randomized, international, open-label trial investigating alectinib vs crizotinib	Peters et al. N Engl J Med. 2017;377:829-838. (primary analysis) (1) Camidge et al. J Thorac Oncol. 2019;14(7):1233-1243. (2) Gadgeel et al. Ann Oncol. 2018;29:2214-2222. (CNS efficacy results) (3)
J-ALEX (Japan)	Phase 3, randomized, multicentre, open-label trial conducted in Japan investigating alectinib vs crizotinib	Hida et al. Lancet. 2017;390:29-39. (primary analysis) (4) Takiguchi et al. J Clin Oncol. 2017;35(no. 15 suppl):9064-9064. (updated analysis) (5) Nishio et al. Lung Cancer. 2018;121:37-40. (CNS efficacy results) (6)
AF-001JP (Japan)	Phase 1/2 trial investigating alectinib conducted in Japan	Seto et al. Lancet Oncol. 2013;14:590-8. (primary analysis) (7) Tamura et al. J Clin Oncol. 2017;35:1515-1521. (three-year follow-up) (8)
	Review and meta-analysis of evidence related to the efficacy and safety of ALK inhibitors (12 studies included).†	Khan et al. Front Oncol. 2019;8:557. (9)
	Network meta-analysis that compared the efficacy and safety of different ALK inhibitors in treating patients with ALK-positive NSCLC.†	Fan et al. Cancer Med. 2018;7:4993-5005. (10)
	Retrospective observational study of 110 ALK+ NSCLC patients treated with TKIs	Pacheco et al. J Thorac Oncol. 2019;14:691-700. (11)

† these papers were reviewed by CaTSoP only.

A full description of these papers can be found in the respective PTAC and CaTSoP papers, as per the attached links below.

PTAC paper	 2018-08 Alectinib ALK+ NSCLC PTAC p
CaTSoP paper	 2019-04 CaTSoP paper_alectinib and

1.6 Review of Clinical Evidence

PTAC reviewed the application at the August 2018 meeting. Further advice was recommended to be sought from the CaTSoP Subcommittee around the special authority access criteria, which was provided at the April 2019 meeting. The CaTSoP recommended special authority is outlined below:

Initial application - only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. *Patient has locally advanced, or metastatic, unresectable, non-small cell lung cancer; and*
2. *There is documentation confirming that the patient has an ALK tyrosine kinase gene rearrangement using an appropriate ALK test; and*
3. *Patient has an ECOG performance score of 0-2.*

Renewal application - only from a medical oncologist or medical practitioner on the recommendation of a relevant specialist. Approvals valid for 6 months for applications meeting the following criteria:

All of the following:

1. *No evidence of progressive disease according to RECIST criteria; and*
2. *The patient is benefitting from and tolerating treatment.*

3. PHARMAC Cost-Utility Analysis

A cost-utility analysis (CUA) was undertaken to estimate the cost-effectiveness of alectinib for ALK-positive NSCLC.

2.2 Scope of Analysis

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

3.1.1 Target Population

The target population for this analysis was defined as patients with untreated non-small cell lung cancer with ALK mutation.

3.1.2 Comparator

The comparator(s) used in the analysis was platinum based chemotherapy.

2.3 Model Structure

A copy of the model used for this proposal can be accessed from the following link, and is also available on the internal FD drive. This model is a modified version of PHARMAC's global lung cancer model developed for the entire lung cancer oncology landscape. The modified version has been focussed solely on the target population relevant to this proposal.

3.2.1 Time Horizon

The time-horizon of the CUA was 20 years. Each Markov cycle was one week.

All costs and benefits were discounted at 3.5%.

3.2.2 Model Structure

The model included the following health states:

- Progression Free Survival (PFS)
- Progressed disease (PD)
- Dead

The progression between each of these health states is illustrated in Figure 1 below.

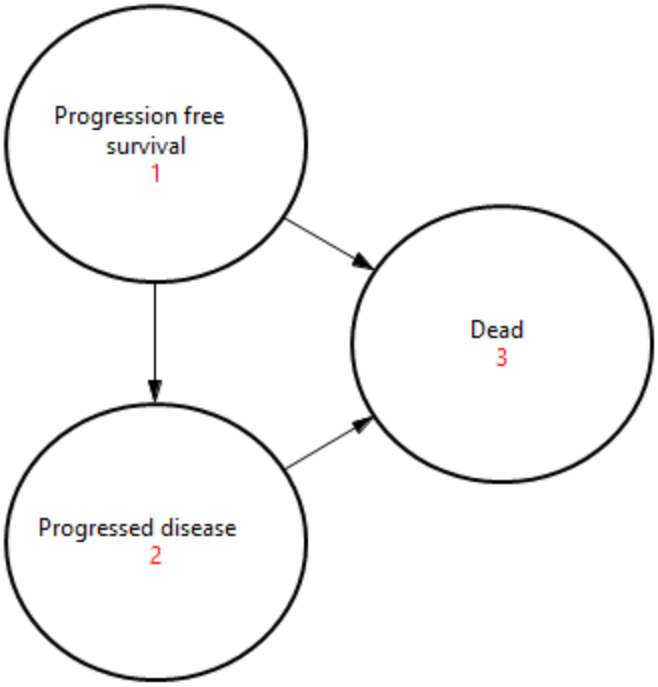

Figure 1. State transition diagram

All patients in the model start in the PFS health state. If clinical evidence of tumour progression occurs at the end of the cycle, these patients switch to using the second line of funded treatment, and so remain in the PFS health state. Only once the patient has exhausted treatment options do they transition to the PD health state, where they remain without treatment. Once patients reach the PD health state, they can either remain here or progress to death at the end of each cycle. Patients can also progress directly from PFS to death, effectively bypassing PD. No patient can transition from PD to PFS.

Patients managed in the interventional arm of the model have three lines of therapy before progressing to the PD health state: alectinib, platinum doublet chemotherapy (cisplatin + gemcitabine) with pemetrexed maintenance, and finally docetaxel chemotherapy. Patients managed in the comparator arm of the model have two lines of therapy: platinum doublet chemotherapy with pemetrexed maintenance, then docetaxel chemotherapy.

2.4 Transformation and Extrapolation of Clinical Evidence

The relative difference in the overall survival and progression free survival for patients managed on alectinib versus the comparator drives this economic model. The modelled values for each of the alternative treatments is shown in Table 3 below.

Table 3. Modelled values for progression free survival and overall survival for each of the alternative therapies considered in this CUA.

Treatment	PFS	OS	Source
Alectinib	34.8 months	50 months	(2)
Platinum doublet with pemetrexed maintenance	4.9 months	11.3 months	(12)
Docetaxel	2.4 months	7 months	(13)
Placebo	N/A	4.6 months	(13)

Note: PFS; progression free survival, OS; overall survival.

- Alectinib survival data has been derived from the updated analysis for the ALEX trial, which has reported a median PFS of 34.8 months (2). OS data has yet to be published for any study involving ALK+ NSCLC patients. Instead, transformation of interim survival data from the ALEX trial has informed the estimated OS of 50 months for alectinib treated patients, discussed further below. This represents the greatest uncertainty in the model, hence has been tested during sensitivity analysis.

- The modelled PFS and OS input values for patients managed on platinum doublet are 4.9 months and 11.3 months respectively. This has been informed by the control arm of a recent phase III RCT comparing the efficacy of pembrolizumab versus platinum chemotherapy with pemetrexed maintenance as first line therapy for 616 patients with metastatic NSCLC (12)[2].

- The modelled PFS and OS input values for patients managed on docetaxel are 2.4 months and 7 months respectively. This has been informed by a phase II RCT comparing the efficacy and safety of docetaxel versus best supportive care for 103 patients with NSCLC who have previously been managed with platinum-based chemotherapy (13).

- The modelled OS input value for patients who had no further lines of therapy available to them is 4.6 months. This was informed by the same phase II RCT from which the survival data for docetaxel was derived (13).

[2] In undertaking a rapid appraisal of this proposal, the generic NSCLC model has been adapted for purpose in assessing alectinib for a genomic subset (ALK+) of the wider NSCLC population for expediency. This introduces a limitation into the model as it therefore relies on an indirect comparison of PFS / OS outcome data between the treatment arms. Should more detailed future analyses be undertaken for this genomic subgroup, clinical efficacy data specific to this target population would strengthen the certainty of modelled outcomes.

3.3.1 Clinical Parameter Estimates

The transitional probabilities as used in this model were calculated by using the above PFS and OS values as follows:

- The formula used to calculate probability of disease progression on each therapy was: probability of progression = $1 - 2e^{(-\frac{1}{PFS})}$
- The formula used to calculate probability of death on each therapy was: probability of death = $1 - 2e^{(-\frac{1}{OS})}$
- An additional transitional probability was calculated to account for the rate of adverse events occurring on each treatment.

These calculated clinical parameters are outlined in Table 4 below.

Table 4. Transition probabilities used in this CUA.

Input	Estimate	Source(s)
PFS on alectinib (prior to 2L treatment with platinum)	0.00462	Based on PFS of 34.8 months (2)
PFS on platinum with pemetrexed (prior to 3L treatment with docetaxel)	0.03236	Based on PFS of 4.9 months (12)
PFS on docetaxel (prior to PD health state)	0.06330	Based on PFS of 2.4 months (13)
PFS to Death (alectinib)	0.00322	Based on OS 50 months (2)
PFS to Death (platinum with pemetrexed)	0.01416	Based on OS 11.3 months (12)
PFS to Death (docetaxel)	0.02277	Based on OS 9.6 months (13)
PD to Death	0.03679	Based on OS 4.3 months (13)

Note: this are weekly probabilities.

The original generic PHARMAC lung cancer model was constructed with the additional consideration of adverse events and treatment discontinuation for each line of therapy. However, following testing of the modified model to inform this updated analysis, it was found that neither of these variables had a meaningful impact on model outcomes. Consequently, these variables were removed from the updated model.

3.3.2 Transformation of alectinib survival data to calculate overall survival

Survival data for alectinib is currently immature. The most recent results reported in the updated analysis of the ALEX trial provided Kaplan Meier overall survival estimates in the supplementary analysis (2)[3]. Median overall survival was not reached at time of manuscript preparation for this analysis. However, this information is still useful. PHARMAC staff have reproduced this survival estimate using plot digitiser software, as shown in Figure 2 below. By applying a linear trendline (shown in the graph below as a blue line) to the obtained survival estimate, the median overall survival for alectinib has been estimated to be 50 months. An exponential trend line (shown in the graph below as a red line) was also fitted, suggesting PFS might reasonably extend beyond 50 months. This parameter was tested during sensitivity analysis[4].

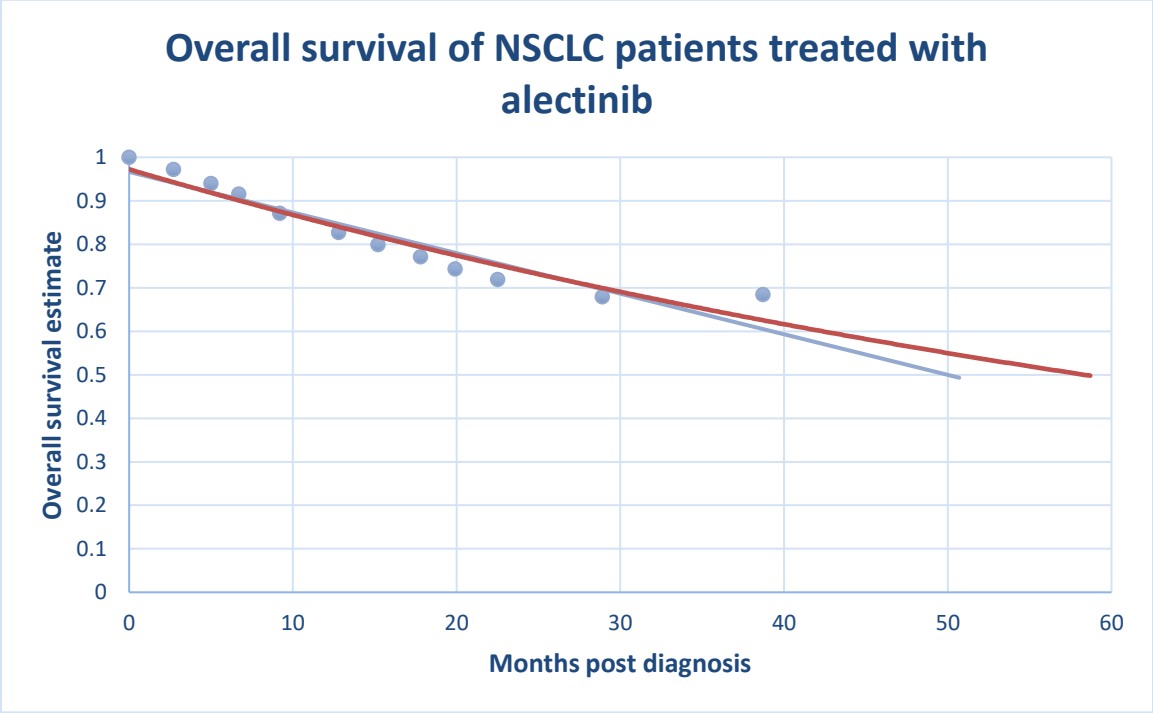

Figure 2. Overall survival estimates for alectinib treated patients; based on supplementary Kaplan Meier estimates from Camidge et al, 2019 (2).

[3] See supplementary figure 4.
[4] The use of median survival data (rather than mean) in this model likely understates the survival benefit of the intervention. Consequently, it can be considered that the reported outcomes of this model represent conservative cost-effectiveness estimates.

2.5 Health-Related Quality of Life

Utility values as used in this model are outlined in

Table 5 below.

Table 5. Utility values used in this CUA.

Health State	Utility	Source
PFS (on chemotherapy)	0.74	(14)
PFS (on alectinib)	0.82	(15)
Progressed disease	0.59	(14)

Progression free survival on chemotherapy and progressed disease

These utility values were informed by a study recommended by PTAC that assessed the health-related quality of life (HRQOL) for advanced NSCLC patients (14). This prospective study was conducted across 25 hospitals in Europe, Canada, Australia and Turkey, using the EuroQOL (EQ-5D) questionnaire and EQ-visual analog scoring. Survey data from 263 patients informed the final results.

Progression free survival on alectinib

This utility value was informed by a study provided within the supplier application that assessed the HRQOL for advanced NSCLC patients in Ontario, Canada (15). Patients included in this study were genotyped for molecular alterations, including ALK+, allowing the effect of both mutation and alternate therapies on HRQOL to be considered in this distinct subpopulation of NSCLC patients. HRQOL for ALK+ve patients in a PFS health state was found to be higher when managed on a tyrosine kinase inhibitor, compared to when these patients were managed on chemotherapy (p=0.04). Hence, it was considered appropriate to include a higher utility value for patients managed with alectinib in our model than for patients managed with chemotherapy. This variable was tested during sensitivity analysis.

2.6 Costs

3.5.1 Pharmaceutical Cost

The pharmaceutical cost of pembrolizumab, platinum-based chemotherapy and docetaxel are outlined in Table 6 below.

Table 6. Pharmaceutical costs included in this CUA.

Pharmaceutical	Pharmaceutical cost	Dosage	Dose (BSA 1.92m^2)	Cost per dose
Alectinib	$7,935 per 224 tablet pack; containing 150mg tablets S 9(2)(b)(ii), 9(2) S 9(2)	600mg twice daily	1200mg	$283.39 / day S 9(2)(b)
Pemetrexed	$217.77 per 500mg vial	500mg/m^2	960mg	$418
Cisplatin*	$21.00 per 100mg vial	75mg/m^2	144mg	$30
Gemcitabine*	$15.89 per 1g	1250mg/m2	2400mg	$47.67
Docetaxel*	$0.62 (10mg per ml, 2ml vial)	75mg/m^2,	144mg	$89
* vial sharing assumed				

* May 2018, Roche Products (New Zealand) Ltd.

Alectinib

The pharmaceutical cost per dose for alectinib is outlined in Table 6. This has been informed by the latest price offer provided by the Supplier as of August 2019. The recommended dose has been informed by the supplier application to PHARMAC in May 2018.

Platinum-based chemotherapy

For non-squamous NSCLC patients, it was assumed that the platinum-based chemotherapy would be pemetrexed with cisplatin[5]. The pharmaceutical cost per dose for

[5] Note: currently funded platinum-based chemotherapies are carboplatin and cisplatin. Carboplatin was not considered due to the complications of costing associated with area under the curve dosing. The cost of carboplatin to cisplatin was not considered to differ significantly.

both pemetrexed and cisplatin is outlined in Table 6. The dose was modelled to be a five hour infusion every three weeks (21-days) as recommended by MedSafe and EviQ (New South Wales Government – Cancer Protocols). Cisplatin is only administered with pemetrexed for the first six cycles. For each subsequent cycle only pemetrexed was administered as per the pemetrexed special authority criteria.

Very few patients with squamous NSCLC cancer are anticipated to be treated with alectinib. Platinum based chemotherapy for squamous NSCLC patients also includes gemcitabine. The pharmaceutical cost of gemcitabine per dose as outlined in Table 6 above is relatively small, and would be even less so when weighted for the anticipated number of squamous relative to non-squamous patients for which we would expect to be treated with alectinib. Consequently, the gemcitabine pharmaceutical cost was removed from the model.

Docetaxel

The modelled dose of docetaxel is 75mg/m^2 as a 1.5-hour infusion, every three weeks. The pharmaceutical cost per dose for docetaxel is outlined in Table 6.

3.5.2 Pharmacy Fees

Alectinib is an oral medication that is intended to be dispensed in the community. Consequently, listing of alectinib will incur a distribution fee equivalent to 4% of the list price. This cost was included in the model.

3.5.3 Health Sector Costs

Additional health sector costs included in the model are outlined in Table 7 below.

Table 7. Health sector costs included in this CUA.

Admin Factor	General cost	Alectinib	Docetaxel	Platinum chemo / Pemetrexed
Infusion costs (quantity used per cycle of treatment)				
Bed time	$65 per hour	0	1.5	5
Nurse time	$55 per hour	0	1.5	5
Preparation	$20 per infusion	0	1	1
Dispensing	$50 per hour	0	0.25	0.25
Reoccurring other health service costs (every 13 weeks)				
Oncologist time	$362 per attendance	1	1	1
CT scan	$769 per scan	1	1	1
One-time other health service costs				
Terminal care	$6,159 per death	1	1	1
ALK testing	$8000 per patient	1	0	0

Chemotherapy infusion costs

All patients receiving platinum and docetaxel chemotherapy require outpatient attendance at a day stay oncology unit to receive this intravenous therapy. This was calculated based on the composite cost of an outpatient bed ($65/hr), nurse ($42/hr), dispensing fee ($50/hr), and preparation ($20/per infusion). The infusion time for patients receiving platinum chemotherapy was estimated to be 5 hours, whereas infusion time for patients receiving docetaxel was estimated to be 1 hour.

Oncologist outpatient visits

It was assumed that patients would continue to attend regular 3 monthly outpatient clinic appointments with an Oncologist whilst remaining on therapy. This cost has been informed from DRG codes.

Scanning costs

All patients are assumed to undergo a six-monthly computerised tomography scan of the chest whilst remaining in the PFS health state. This was informed by the proposed renewal criteria as proposed in the special authority for alectinib.

Terminal care costs

We have used a terminal care cost of $6,159, which is applied when patients transition from either of the alive states (PFS and progressed disease) to death. The supplier's terminal care cost is the figure published by the University of Otago's BODE3 group, derived from the Ministry of Health's Health Tracker analysis of cancer treatment costs.

ALK testing

Listing of alectinib will result in a new requirement on DHBs to provide testing for the ALK oncogene in all NSCLC patients, involving ~800 patients per annum. Weighted across the 40 expected patients within the target population, an additional one-time cost per patient in the intervention arm of $8000 has been added to the model. This variable was tested during sensitivity analysis given the uncertainty of the number of patients each year that will have this test completed.

Excluded health sector costs

The model does not consider any cost in the monitoring and treatment of adverse events. This is due to the uncertainty around the incremental quantity of health service resources this would require between the treatment and the comparator.

2.7 Cost-Effectiveness Results

The incremental cost is estimated to be [redacted], with a QALY gain of 2.22. The estimated QALYs per $1million is therefore [redacted] cost per QALY of [redacted]. This is shown in Table 8 below.

Table 8. Cost-effectiveness results.

	Platinum chemotherapy	Alectinib	Incremental
QALYs	0.57	2.79	2.22
Cost	$17,652	[redacted]	[redacted]
QALYs per $1m			[redacted]

2.8 Sensitivity Analysis

Selected results from one-way deterministic sensitivity analysis are presented in Table 9 below.

Table 9. Sensitivity analysis.

Input	Base-Case Value	Low Value	High Value	Range QALYs per $m
QOL weighting of alectinib patients in PFS	0.82	0.74	0.82	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)
QOL weighting of platinum and docetaxel patients in PFS	0.74	0.74	0.78	
Overall survival Alectinib +/- 10%	50 months	45	55	
Horizon +/- 10 years	20 years	10	30	
PFS on Alectinib +/- 20%	34.8 months	27.8	41.8	
If ALK testing is provided to double base case estimate (i.e. 800 annual patients x 2)	$8,000 per patient	$8,000	$16,000	
Discount rate	3.5%	0%	5%	

2.9 Summary of Overall Cost-Effectiveness

As outlined above, the base-case QALY per $1m estimate is S 9(2)(b). Taking into account the results of the sensitivity analysis, the highly likely range is estimated to be S 9(2)(b)(ii), 9(2)(ba)(i) &. This range captures the uncertainty of the estimated annual number of NSCLC patients who will undergo ALK testing. The possible QALY per $1m range is S 9(2)(b)(ii), 9(2)(ba)(i) &. This range captures the uncertainty of the appropriate quality of life weight for alectinib patients whilst in the PFS health state.

4. Budget Impact Analysis

The 5-year net present value (NPV) to the Community Pharmaceutical Schedule of funding alectinib is estimated to be S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j), with a cost of the first financial year of S 9(2)(b)(ii), [redacted]. This is outlined in Table 10 below. The 5-year NPV to DHBs is estimated to be S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j). All costs are discounted at a rate of 8%.

Table 10. Net Budget Impact to DHBs.

	Year 1	Year 2	Year 3	Year 4	Year 5	5-Year NPV
Patient numbers	23	50	50	50	50	
Community Pharmaceutical Budget	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					
Hospital Pharmaceutical Budget	$0	$0	$0	$0	$0	$0
Other DHB Costs	$0.19m	$0.32m	$0.32m	$0.32m	$0.32m	$1.25m
Total net budget impact to DHBs	S 9(2)(b)(ii), 9(2)(ba)(i) & 9(2)(j)					

Noting;

1. Listing date is 1st December 2019
2. A cost to other DHB budgets is anticipated as a result of needing to screen all NSCLC patients for the ALK+ve mutation.
    a. The estimated number of patients requiring testing per year is 800.
    b. The estimated cost of ALK mutation testing is $400 per patient.
3. An estimated 40 patients will meet the eligibility criteria for alectinib each year.
4. To account for average duration of treatment (15 months), 50 patients per year have been modelled from year 2 onwards.

5. References

1. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. The New England journal of medicine. 2017;377(9):829-38.
2. Camidge DR, Dziadziuszko R, Peters S, Mok T, Noe J, Nowicka M, et al. Updated Efficacy and Safety Data and Impact of the EML4-ALK Fusion Variant on the Efficacy of Alectinib in Untreated ALK-Positive Advanced Non-Small Cell Lung Cancer in the Global Phase III ALEX Study. Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer. 2019;14(7):1233-43.
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Appendix 1. Changes made to the original model that was used for prioritisation

1. Price of alectinib; this has had the largest bearing on the model, shifting the central estimate by S 9(2) QALYs per $1m.
2. Weighted cost of ALK testing per patient treated; this was not considered in the original model and has been included in this new one; this reduced the central estimate by S 9(2)(b)(ii) QALY per $1m.
3. Pharmaceutical distribution costs for alectinib (based on list price * 4%) has been added to this new model; this has reduced the central estimate by just under S 9(2) QALYs per $1m.
4. The PFS and OS data for both platinum pemetrexed and docetaxel has been updated to reflect the current evidence base best representing the target population; this has had a negligible impact on the model (although has marginally increased the incremental benefit of the intervention as the Docetaxel PFS appeared to have been considerably overstated in the original model i.e. 4.3 months to 10.6 weeks.
5. The probability of having an adverse event and treatment discontinuation was tested during sensitivity analysis and found to have no bearing on the model outcomes. Consequently, these variables have been ignored in this updated model.
6. The greatest uncertainty with the model remains the overall survival for alectinib treated patients, as this data is still immature. The median overall survival has yet be reported. Extrapolation of the most recently presented data suggests this might reasonably be 50 months, which has informed the central estimate. Adding 10% variation around this estimate adjusts the central estimate by S 9(2) QALY.
7. The claimed increase in quality of life for patients managed on alectinib has a significant bearing on the model (0.82 vs 0.74), improving the central estimate by S 9(2) QALYs.
8. The overall survival for patients without further treatment options was increased from (4.7-1.8 = 2.9) months to 4.3 months, in line with the phase II RCT for which the target population was considered most relevant (Sheppard et al). This had a negligible impact on the model.
9. The cost per CT scan has been corrected from $650 to $769 as per the 2018 cost spreadsheet
10. The bed time and nurse time for each of platinum premetrexed and docetaxel were corrected as per the most recent chemotherapy guidelines, referenced above (these were also used in the pembrolizumab TAR). Platinum weighting increased from 0.5 to 5hours. Docetaxel weight increased from 1 to 1.5 hours
11. An extra cost to account for ongoing outpatient oncology visits has been added to the model, equivalent to $362 every 13 weeks.