

Alectinib for Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC): 24 month predicted versus actual analysis

Drug utilisation sub-committee (DUSC)

October 2020

Abstract

Purpose

To compare predicted and actual utilisation of alectinib in stage IIIB (locally advanced) or stage IV (metastatic) non-small cell lung cancer.

Date of listing on the Pharmaceutical Benefits Scheme (PBS)

Alectinib was PBS listed on 1 January 2018.

Data Source / methodology

Data extracted from the PBS data maintained by Department of Health, processed by Services Australia was used for all analyses.

Key Findings

- There were 254 and 322 patients treated with alectinib during the first and second year of listing respectively, which was higher than estimated.
- There were 1,715 and 2,546 alectinib prescriptions dispensed during the first and second year of listing respectively, which was higher than estimated.
- The most common age group in patients beginning alectinib treatment were those aged between 60- 64 years old with 53.1% of initiating patients being female.
- The mean duration of alectinib treatment accounting for breaks in treatment was 13.78 months (95% confidence interval 11.75-15.80 months). The treatment time for alectinib was longer than predicted.
- Most patients have generally initiated on alectinib as first-line anaplastic lymphoma kinase positive non-small cell lung cancer treatment.

Purpose of analysis

To compare predicted and actual utilisation of alectinib in stage IIIB (locally advanced) or stage IV (metastatic) non-small cell lung cancer. At its June 2020 meeting, DUSC suggested a review should investigate whether patients are commencing alectinib after other therapies.

Background

Clinical situation

Lung cancer is one of the most common causes of cancer related death in Australia.¹ Non-small cell lung cancer (NSCLC) is attributed to 80% of all lung cancers.² Alectinib is used to treat adult patients with NSCLC where the cancer cells have a faulty anaplastic lymphoma kinases (ALK) gene, meaning they are ALK-positive. These cancer cells have either progressed into advanced stages or spread to another region of the body (metastatic).³

ALK-inhibitor crizotinib (PBS listed 1 July 2015), is a first-line treatment option for NSCLC. Ceritinib (PBS listed 1 April 2017) is another NSCLC treatment option and offered to patients whose disease has progressed or to patients who are intolerant of crizotinib. Ceritinib however has a boxed warning outlining its safety concerns associated with an unfavourable gastrointestinal profile.⁴ Alectinib was proposed as a preferred treatment option, particularly as it was reported to have greater efficacy and lower toxicity in patients compared to ceritinib.^{5,6} NSCLC disease progression is commonly characterised by metastases in the central nervous system (CNS), particularly in the brain. Unlike crizotinib, alectinib is active in the CNS and would be capable of inhibiting disease progression.^{5,7}

Pharmacology

Alectinib inhibits activity of the ALK protein, which is responsible for the development and spread of cancer cells.³

¹ Australian Institute of Health and Welfare. Cancer data in Australia [Internet]. Canberra: Australian Institute of Health and Welfare, 2020 [cited 2020 Aug. 19]. Available from: <https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia>

² Zarogoulidis K, Zarogoulidis P, Darwiche K, et al. Treatment of non-small cell lung cancer (NSCLC). *J Thorac Dis.* 2013;5 Suppl 4(Suppl 4):S389-S396. doi:10.3978/j.issn.2072-1439.2013.07.10

³ Alecensa (Alectinib) Australian Approved Consumer Medicine Information. Sydney: Roche Products Pty Limited. Approved 14 March 2017. Available from < <https://www.tga.gov.au/consumer-medicines-information-cmi>.>

⁴ Zykadia (Ceritinib) Australian Approved Product Information. Macquarie Park: Novartis Pharmaceuticals Australia Pty Limited. Approved 31 March 2016, updated 16 June 2020. Available from < <https://www.tga.gov.au/product-information-pi>.>

⁵ Peters S, Cambridge DR, Shaw AT, et al. Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer. *N Engl J Med.* 2017;377(9):829-838. doi:10.1056/NEJMoa1704795

⁶ Gadgeel S, Peters S, Mok T, Shaw A-T, Kim D-W, Ou S-I, et al. Alectinib versus crizotinib in treatment-naïve anaplastic lymphoma kinase-positive (ALK+) non-small-cell lung cancer: CNS efficacy results from the ALEX study. *Ann Oncol.* 2018;29(11):2214-2222. doi:10.1093/annonc/mdy405

⁷ Alectinib superior to crizotinib for ALK+ NSCLC, Cancer discovery, 2017 7(8), OF5 DOI: [10.1158/2159-8290.CD-NB2017-090](https://doi.org/10.1158/2159-8290.CD-NB2017-090)

Therapeutic Goods Administration (TGA) approved indications

Alectinib was listed on the Australian Register of Therapeutic Goods on 14 March 2017. Alectinib was only indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC.⁷ Alectinib is restricted to patients who had disease progression on or are intolerant to crizotinib.

The ARTG listing was updated in 30 January 2018 from second-line to line agnostic treatment. Alectinib was indicated for the treatment of patients with ALK-positive, locally advanced or metastatic NSCLC.

Dosage and administration

Alectinib is to be taken orally, 600 mg (4 × 150 mg capsules), twice a day with food with the total daily dose of 1,200 mg.⁸

Alectinib dose modifications apply if patients experience specific adverse events such as Interstitial Lung Disease or Bradycardia. Detailed guidelines for these events can be found in the Product Information.

The current Product Information (PI) and Consumer Medicine Information (CMI) are available from [the TGA \(Product Information\)](#) and [the TGA \(Consumer Medicines Information\)](#).

PBS listing details (as at August 2020)

Table 1: PBS listing of alectinib

Item	Name, form & strength, pack size	Max. quant.	Rpts	DPMQ	Brand name and manufacturer
11226W	Alectinib 150 mg capsules in blister multipacks (4 packs of 56) ⁹	Pack: 1 Units: 224	3	\$6830.04	Alecensa Roche Products Pty Ltd

Note: No increase in the maximum quantity or number of units may be authorised.

Note: No increase in the maximum number of repeats may be authorised.

Note: Special Pricing Arrangements apply.

Source: the [PBS website](#).

Restriction

Alectinib is an Authority Required (Telephone) PBS medicine.

⁸ Alecensa (Alectinib) Australian Approved Product Information. Sydney: Roche Products Pty Limited. Approved 14 March 2017. Available from < <https://www.tga.gov.au/product-information-pi>.>

⁹ Alecensa (Alectinib) Australian Approved Consumer Medicine Information. Sydney: Roche Products Pty Limited. Approved 14 March 2017. Available from < <https://www.tga.gov.au/consumer-medicines-information-cmi>.>

Table 2: Clinical and population criteria according to patient's treatment phase

Treatment Phase	Clinical criteria	Population criteria
Initial treatment	The treatment must be as monotherapy, AND The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND Patient must have a WHO performance status of 2 or less	Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH testing)
Continuing treatment	The treatment must be as monotherapy, AND Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition	
Grandfathering treatment	Patient must have previously received non-PBS-subsidised treatment with this drug for this condition prior to 1 January 2018, AND The treatment must be as monotherapy, AND The condition must be non-squamous type non-small cell lung cancer (NSCLC) or not otherwise specified type NSCLC, AND Patient must have a WHO performance status of 2 or less, AND Patient must not have progressive disease while receiving treatment with this drug for this condition	Patient must have evidence of an anaplastic lymphoma kinase (ALK) gene rearrangement in tumour material, defined as 15% (or greater) positive cells by fluorescence in situ hybridisation (FISH testing). A patient may qualify for PBS-subsidised under this restriction once only. For continuing PBS-subsidised treatment, a Grandfathered patient must qualify under the Continuing treatment criteria

For details of the current PBS listing refer to the [PBS website](#).

Date of listing on PBS

Alectinib was PBS listed on 1 January 2018.

Changes to listing

The number of repeats have increased from one to three as of July 2020.

On 23 August 2019, the Medical Oncology Group of Australia (MOGA) requested the PBAC to consider increasing the number of repeats for alectinib from one to three. The MOGA noted increasing the number of repeats would allow alectinib to align with other antineoplastic agents for NSCLC such as erlotinib which is currently listed with three repeats. The MOGA highlighted the increase in the number of repeats would allow patients more flexibility of follow-up with their oncologists as appointments were not required every two months. In the November 2019 PBAC Meeting, the PBAC recommended an increase in the number of repeats for the Authority Required listings for alectinib for Stage IIIB (locally advanced) or Stage IV (metastatic) NSCLC from one to three.

Current PBS listing details are available from the [PBS website](#).

Approach taken to estimate utilisation

A “Mixed model” approach was used where both epidemiological and market-share approaches were taken into account to estimate utilisation.

Epidemiological approach:

The epidemiological approach aimed to estimate the number of patients whose disease would progress on a prior ALK-inhibitor and would initiate treatment with alectinib per year.

Based on the favourable efficacy and safety profile of alectinib compared to ceritinib and advice from the clinician advisory board, the Budget Impact Assessment (BIA) estimated alectinib would obtain 90% of the second-line ALK-inhibitor market in 2018 and 100% of the market thereafter. Hence, 131 patients were estimated to be treated with alectinib in 2018.

30 patients involved in Roche’s patient access program were eligible to be grandfathered to the PBS-listed alectinib. The BIA estimated these 30 grandfathered patients would receive the full course of alectinib treatment through the PBS in the first year of listing.

Market-share approach

The market-share approach aimed to estimate the size of the second-line ALK-inhibitor market based on the number of scripts processed for crizotinib in 2016.

The number of items processed for crizotinib for the full calendar year of 2016 was used as a basis for estimating the market for crizotinib failure patients. A total of 1,221 PBS and RPBS items were processed for crizotinib from January 2016 to December 2016. The total number days of crizotinib treatment dispensed in 2016 and median duration of treatment on crizotinib were ascertained from literature (Shaw et al, 2013). In 2016, 169 patients were estimated to be treated with crizotinib.

This estimate was consistent with the epidemiological utilisation estimate of 178 patients in 2016. The difference of nine patients is equivalent to a percentage difference of 5%, indicating a conservative estimate of the ALK-inhibitor market was taken using the epidemiological approach.

A mean duration of progression free survival of 11.64 months was calculated. Doses (capsules per treatment) and scripts per course of treatment were calculated to determine the script substitution rate of alectinib with ceritinib. 1.07 scripts of alectinib would be dispensed for every script of ceritinib displaced by alectinib.

Relevant aspects of consideration by the Pharmaceutical Benefits Advisory Committee (PBAC)

July 2017 PBAC Meeting

PBAC recommended an Authority Required listing of alectinib for the treatment of patients with ALK-positive NSCLC. The restriction criteria for alectinib would be made similar to ceritinib, of Authority Required (Telephone) without restrictions to the line of therapy.

A cost-minimisation against ceritinib was accepted based on the submission's reasonable claim of non-inferiority for efficacy and safety against ceritinib.

The submission proposed alectinib as a second line therapy after crizotinib. However, the PBAC acknowledged the evidence presented in the submission was in a different setting. The PBAC recommended ceritinib without restrictions to the line of therapy as the evidence presented in the submission was in a different setting (ceritinib [Public Summary Document](#), November 2016 PBAC meeting). Based on this, the PBAC recommended the restriction for alectinib be in close alignment with the current PBS listing for ceritinib: a telephone Authority listing without any restrictions to the line of therapy.

A naïve indirect comparison between two pooled single arm alectinib (NP28761 & NP28673) and ceritinib (ASCEND-1 & ASCEND-2) studies were presented in the submission. The difference in point estimates of median progression free survival (IRC assessed) and median overall survival both favoured alectinib. Despite the possible confounding in post-progression therapies between studies and survival data being relatively immature, the PBAC considered the submission's claim of non-inferior comparative effectiveness against ceritinib was acceptable.

The PBAC noted the different side effect profiles associated with ceritinib and alectinib based on the data presented in the submission. Ceritinib was associated with higher incidence of Grade 2-4 diarrhoea, nausea and vomiting whereas alectinib was associated with higher incidence of myalgia and creatinine phosphokinase elevation. Cases of severe interstitial lung disease/pneumonitis were reported in both drugs. Although the currently available clinical data was insufficient to completely define the safety profile of alectinib, the PBAC noted it was acceptable to conclude alectinib was non-inferior in terms of safety compared to ceritinib.

The mean treatment duration with ceritinib was likely to be shorter than mean treatment duration with alectinib as the median progression free survival (PFS) in the ceritinib studies (5.4-7.2 months) was shorter than in alectinib studies (8.3 months). The PBAC recommended the differential duration of therapy be accounted in calculating the cost-minimisation against ceritinib. The mean PFS in Australia (second-line to a prior ALK-inhibitor) may be longer than observed in studies, where the majority of patients have previously been treated with both crizotinib and chemotherapy. ESC noted the clinical place of alectinib would affect mean duration of treatment and thus its financial implications.

The PBAC noted the mean number of scripts per patient and the mean cost per patient for a course of alectinib would likely be higher than estimated in the submission as the mean duration of treatment based on the estimated PFS in clinical studies is likely to underestimate the mean duration of treatment in clinical practice.

The mean duration of ceritinib treatment was assumed to be the same as alectinib (i.e. the mean PFS in alectinib studies). As the median PFS in the ceritinib studies (5.4-7.2 months) was numerically shorter than the median PFS in the alectinib studies (8.3 months), there is potential for the mean duration of treatment with ceritinib to be shorter than the mean duration of treatment with alectinib.

The submission did not take dose reductions for management of adverse events into account, despite highlighting the extent of dose reductions required with ceritinib in the submission. Therefore, the submission may have overestimated the cost off-sets resulting from substitution for ceritinib.

The PBAC advised the effective price for alectinib be no higher than the effective price for ceritinib based on the cost per day of treatment. Alectinib 600mg (4 × 150 mg capsules) twice daily and ceritinib 750 mg (5 × 150 mg capsules) daily would be equi-effective doses, accounting for the different durations of therapy.

The PBAC rejected crizotinib as a comparator for alectinib, as crizotinib requires written authorisation to be obtained for PBS subsidy, and would therefore be less likely to be used.

The PBAC noted the financial estimates presented in the submission were overestimated as the uptake rate of ceritinib since its PBS listing on 1 April 2017 was substantially lower than predicted in its submission. PBAC advised the financial estimates of alectinib would need to be revised based on the PBAC'S recommendation of not restricting the line of therapy. The revised estimates should account for grandfathered patients in the sponsor's patient access program.

For further details, refer to the [Public Summary Document](#) from the July 2017 PBAC meeting.

March 2019 PBAC Meeting

The PBAC rejected requests from patients and healthcare professionals to lower restrictions from Authority Required (Telephone) to Authority Required (STREAMLINED) and to increase repeats from one to five. As alectinib was recently listed on the PBS (1 January 2018), the PBAC commented on the need for a longer period of utilisation data to ensure cost effectiveness in the current patient population.

The PBAC noted stable patients on continuing treatment were required to schedule medical appointments to obtain prescriptions and increasing the number of repeats would be beneficial for these patients. However, the PBAC noted increasing repeats from one to five could inappropriately extend the treatment duration in some patients, with the risk of

continuing an ineffective treatment and/or unmanaged toxicity with the impact on cost effectiveness of extended treatment being unclear.

The PBAC acknowledged the possibility for future requests to be considered once the ALK-inhibitor market has stabilised and long-term PBS utilisation data (of at least 24 months) is available for alectinib.

For further details, refer to the [Public Summary Document](#) from the March 2019 PBAC meeting.

November 2019 PBAC Meeting

In August 2019, the Medical Oncology Group of Australia (MOGA) wrote to the PBAC requesting an increase of in the number of repeats from one to three to align with similar antineoplastic agents for NSCLC. The MOGA noted the increase in the number of repeats would allow patients with greater flexibility of follow up with their oncologists as appointments weren't required every two months. At the November 2019 PBAC meeting, the PBAC recommended an increase in repeats from one to three to be consistent with current listings for antineoplastic agents.

In the November 2019 PBAC meeting, the PBAC recommended two new items for ALK positive NSCLC: brigatinib and lorlatinib.

The PBAC recommended brigatinib to be Authority Required listed for stage IIIB (locally advanced) and stage IV (metastatic) ALK- positive non-squamous (NS) or not otherwise specified (NOS) NSCLC and was cost-minimised against alectinib. Brigatinib was PBS listed in May 2020.

The PBAC recommended lorlatinib to be Authority Required listed for stage IV (metastatic) NSCLC who have disease progression either following treatment with crizotinib and at least one other ALK tyrosine kinase inhibitor (TKI) or following an ALK-TKI other than crizotinib (second-line and subsequent-line settings). The PBAC recommended lorlatinib due to the high unmet clinical need for effective treatments and broader mutational coverage and intracranial activity. Lorlatinib was cost minimised against alectinib and was PBS listed in August 2020.

For further details, refer to the [Public Summary Document](#) from the November 2019 PBAC meeting.

Methods

Data extracted from the PBS data maintained by Department of Health and processed by Services Australia was used for all analyses. Prescription data was extracted from when alectinib was PBS listed, 1 January 2018 up to and including 30 June 2020. Prescription data from when crizotinib was PBS listed, 1 July 2015, up to and including 30 June 2020 was extracted to compare utilisation rates of ALK-inhibitors crizotinib and ceritinib to alectinib. Data was extracted on 7 August 2020.

This data was used to determine the number of incident and prevalent patients, number of prescriptions supplied and to analyse patient demographics such as age, gender and clinician trends. Initiating and prevalent patients were counted by quarter of supply. An initiating patient was defined based on first date of supply of alectinib. Quarterly market share from July 2015 (the PBS listing date of crizotinib) on were extracted to analyse trends in crizotinib, ceritinib, alectinib and brigatinib.

A drug sequence analysis was conducted to examine the pattern of ALK utilisation in patients. Two cohorts were selected for this analysis to compare therapy patterns before and after alectinib was PBS listed. The first cohort were patients who were followed from when crizotinib was PBS listed to before alectinib was PBS listed, July 2015 to December 2017. The second group were patients who were followed from when crizotinib was PBS listed to analysis end date, July 2015 to June 2020. In both of these cohorts, the first prescribed drug was recorded and if patients were subsequently supplied other drugs, these were noted to form the patient's drug chronological sequence.

The treatment duration of alectinib was ascertained to compare the submission's initial estimates of alectinib being cost minimised to ceritinib based on length of treatment. Median supply days for alectinib and ceritinib were calculated. A Kaplan Meier curve was generated to present treatment duration, censoring patients that were still continuing treatment at the analysis end date. A cohort of initiating patients were selected from 1 April 2018, to account for the wash out period of grandfathered patients, up to and including 31 October 2018. These patients were followed until 30 June 2020.

Another Kaplan Meier curve was generated accounting for breaks in treatment. A patient was considered to be on a treatment break if they did not receive a supply in more than two sets of standard treatment days. The median standard treatment days was calculated to be 29 days. Typically, patients are considered to be on break if they missed more than three sets of standard treatment days. However, as a cancer treatment, it was assumed that patients taking alectinib would be more closely managed by their prescribers, increasing treatment adherence and reducing the likelihood for breaks.

As this analysis uses date of supply prescription data, there may be small differences compared with publicly available Services Australia Medicare date of processing data.¹⁰ The publicly available Medicare data only includes subsidised R/PBS prescriptions with

¹⁰ PBS statistics. Australian Government Department of Human Services Medicare. Canberra. Available from <<http://www.medicareaustralia.gov.au/provider/pbs/stats.jsp>>.

prescriptions under the patient co-payment not included. The Medicare data used in this report includes under co-payment prescriptions from 1 April 2012.

Data manipulation was undertaken using SAS.

Results

Analysis of drug utilisation

Overall utilisation

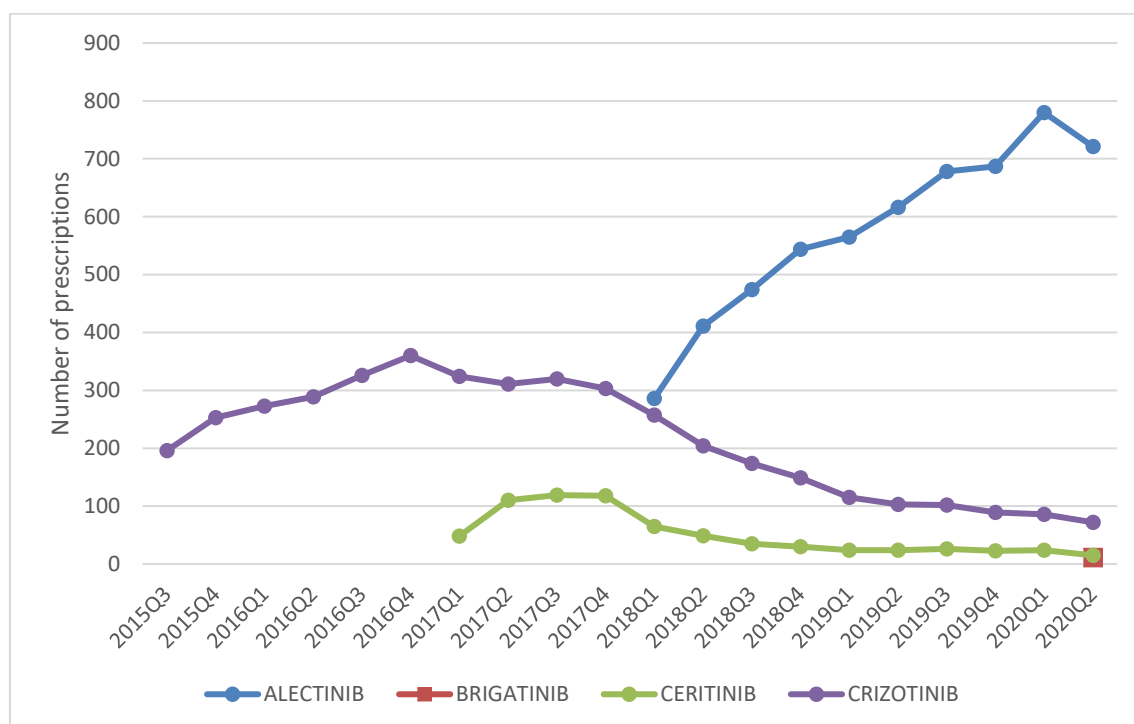


Figure 1: Number of alectinib, brigatinib, ceritinib and crizotinib prescriptions supplied

Figure 1 shows the number of ALK-inhibitor scripts dispensed since crizotinib was first PBS listed, July 2015 to June 2020. There has been a large increase in the number of alectinib prescriptions dispensed from when it was PBS listed on 1 January 2018. In its first supply quarter, the number of alectinib prescriptions dispensed was more than twice that of ceritinib. Once alectinib was introduced to the market, there was an evident decrease in the number of ceritinib and crizotinib prescriptions dispensed. Ceritinib averaged at approximately 115 scripts per supply quarter from when it was PBS listed, but decreased averaging at 32 scripts in subsequent supply quarters once was alectinib was PBS listed. Crizotinib averaged at approximately 250 scripts per supply quarter from when it was PBS listed, but decreased to 100 scripts in subsequent supply quarters following alectinib listing. Brigatinib was PBS listed in May 2020 during the second quarter of 2020, with the number of prescriptions dispensed similar to that of ceritinib.

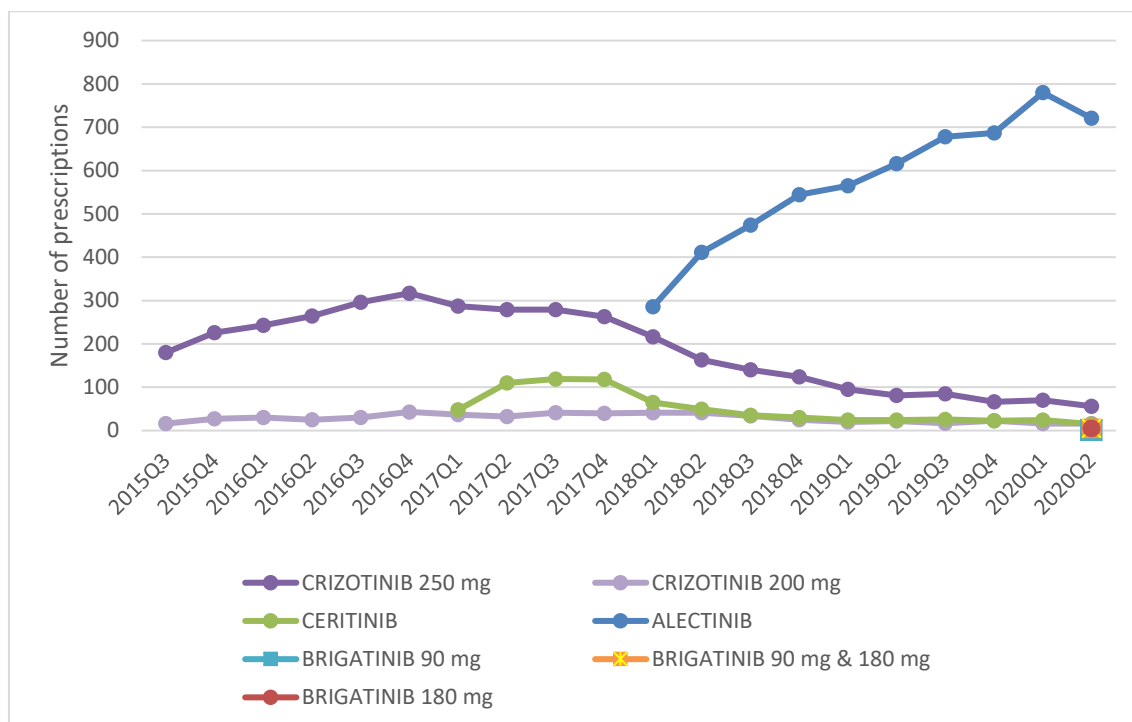


Figure 2: Number of alectinib, brigatinib, ceritinib and crizotinib prescriptions supplied by strength

Figure 2 shows the number of prescriptions dispensed according to strength. Both alectinib and ceritinib only have one strength listed on the market, 150 mg. Crizotinib has two strength variations: 200 mg and 250 mg. Newly listed brigatinib has four strengths PBS listed: 30 mg, 90 mg, 180 mg and 90 mg & 180 mg. However, only the 90 mg, 180 mg and 90 mg & 180 mg variations were supplied during the second quarter of 2020. Since crizotinib was PBS listed, supplies of the 200 mg variant plateaued averaging at less than 50 scripts each supply quarter. This is in contrast to the 250 mg variant, which accounted for majority of crizotinib supply. 196 scripts were dispensed in its first supply quarter, reaching its peak at 360 scripts in the fourth supply quarter of 2016. The number of prescriptions dispensed by all three strengths of brigatinib dispensed in the second quarter of 2020 were lower compared to ceritinib.

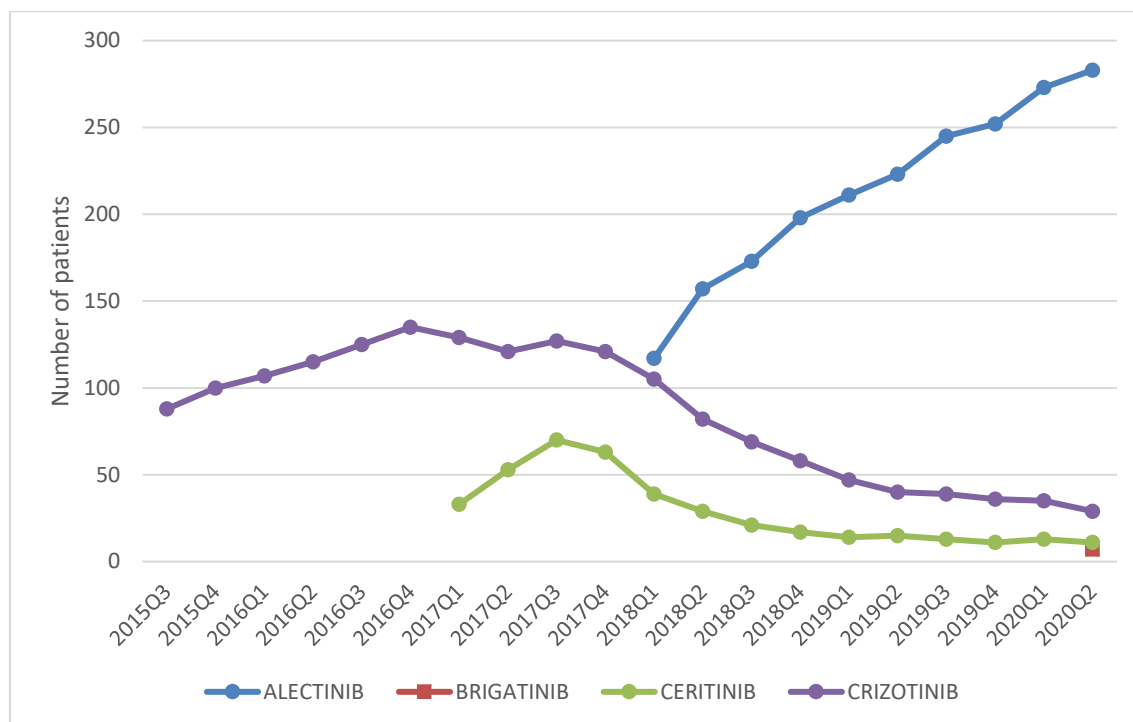


Figure 3: Number of patients treated with alectinib, brigatinib, ceritinib and crizotinib

Similar to Figure 1, there has been a large increase in the number to alectinib patients since it was PBS listed on 1 January 2018. Once alectinib was introduced to the market, there was an evident decrease in the number of ceritinib and crizotinib patients. An average of 48 patients were supplied ceritinib each supply quarter from when ceritinib was PBS listed. The number of ceritinib patients appeared to gain traction, however, once alectinib was PBS listed, the number of ceritinib patients decreased to an average of 25 patients in subsequent supply quarters. An average of 105 patients were supplied crizotinib each supply quarter from when crizotinib was PBS listed, but the number of crizotinib patients decreased to an average of 67 patients in subsequent supply quarters once alectinib was PBS listed. Brigatinib was PBS listed in May 2020 during the second quarter of 2020, with the number of patients similar to that of ceritinib.

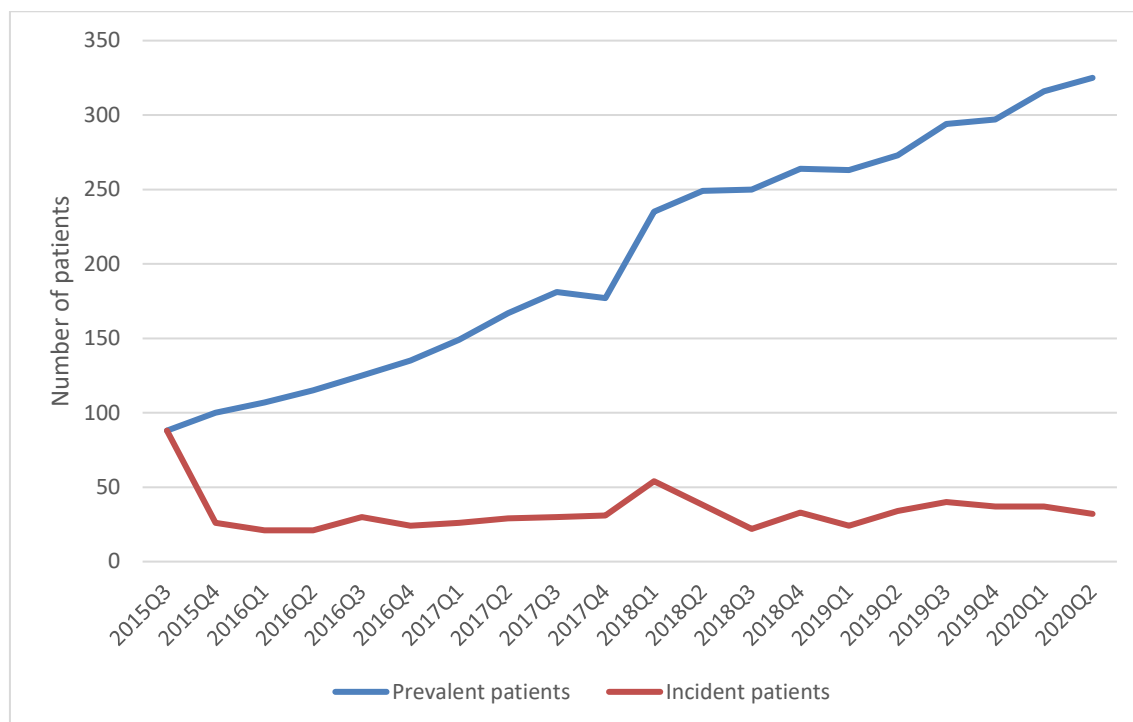


Figure 4: Number of incident and prevalent patients on ALK-inhibitor therapy: alectinib, brigatinib, ceritinib and crizotinib

Figure 4 shows a steady rate of incident patients onto ALK-inhibitor therapy with between 20 to 40 new patients first supplied ALK treatment each supply quarter. A peak of 54 patients was observed when alectinib was PBS listed where it subsequently returned to a steady level. Since the third quarter of 2015 to the second quarter of 2020, the number of prevalent patients undertaking ALK-inhibitor therapy have increased from 88 to 325 patients.

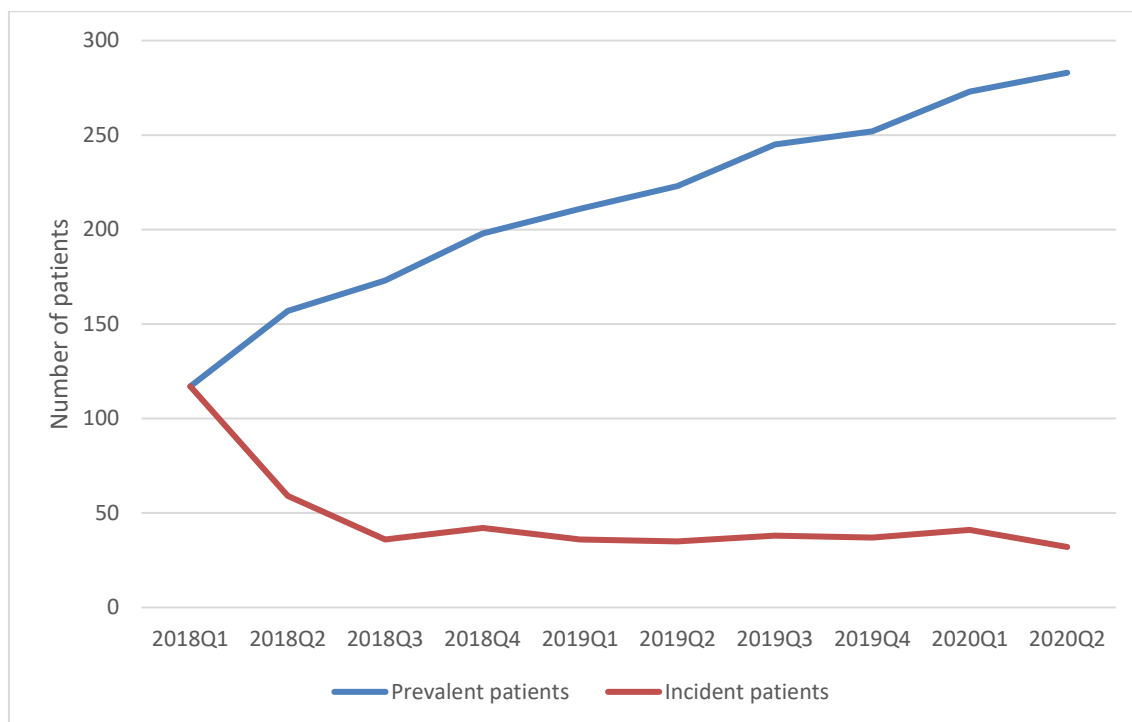


Figure 5: Number of incident and prevalent alectinib patients according to supply quarter

From Figure 5, a linear increase in the number of prevalent patients is observed. A steady rate of 30-45 new patients who are first supplied alectinib in each supply quarter. The number of treated patients has increased from 117 patients in first quarter of 2018 to 283 patients in the second quarter of 2020.



Figure 6: Market share of ALK-inhibitors: alectinib, brigatinib, ceritinib and crizotinib, according to supply quarter

From Figure 6, prior to the PBS listing of alectinib, crizotinib and ceritinib accounted for approximately 70% and 30% of the ALK-inhibitor market, respectively. Following the PBS listing of alectinib, the market share of crizotinib and ceritinib decreased to approximately 65% and 10%, respectively. In 2020, the market share of crizotinib and ceritinib has further decreased to approximately 10% and less than 5%, respectively. On the other hand, the market share of alectinib has increased from 45% when first listed to 90% in 2020.

Brigatinib was PBS listed in May 2020 and based on two months of supply data, it has accounted for less than 5% of the ALK-inhibitor market. This is in stark contrast to alectinib, which accounted for approximately 45% of market share in its first supply quarter.

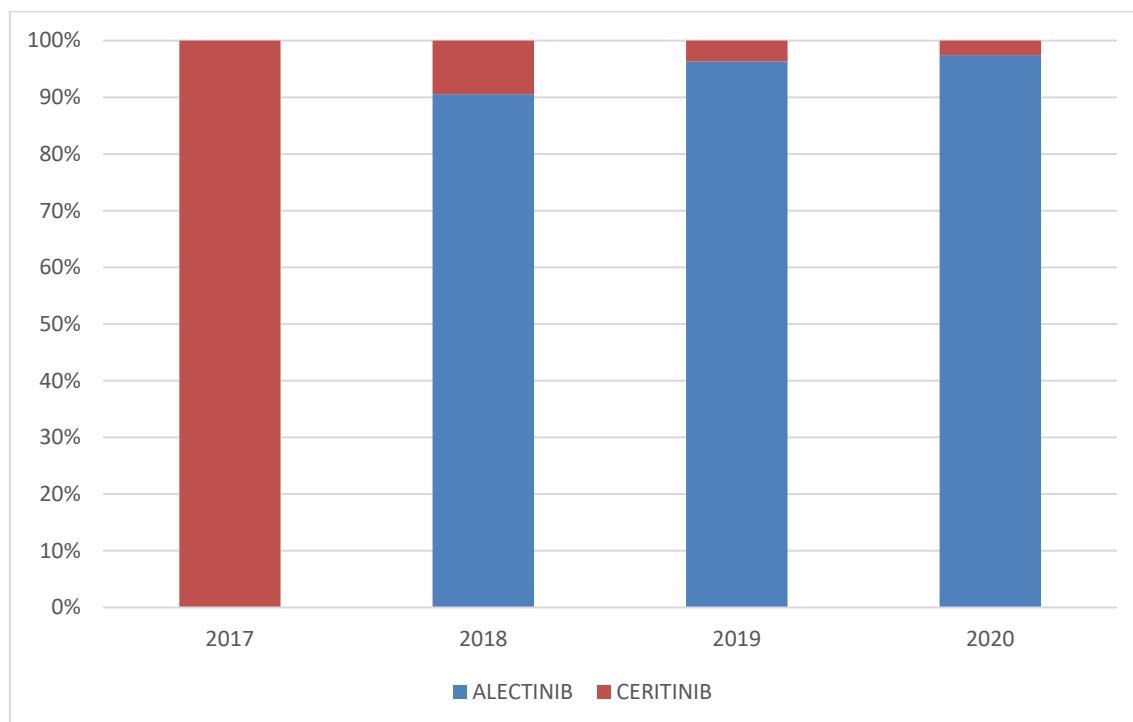
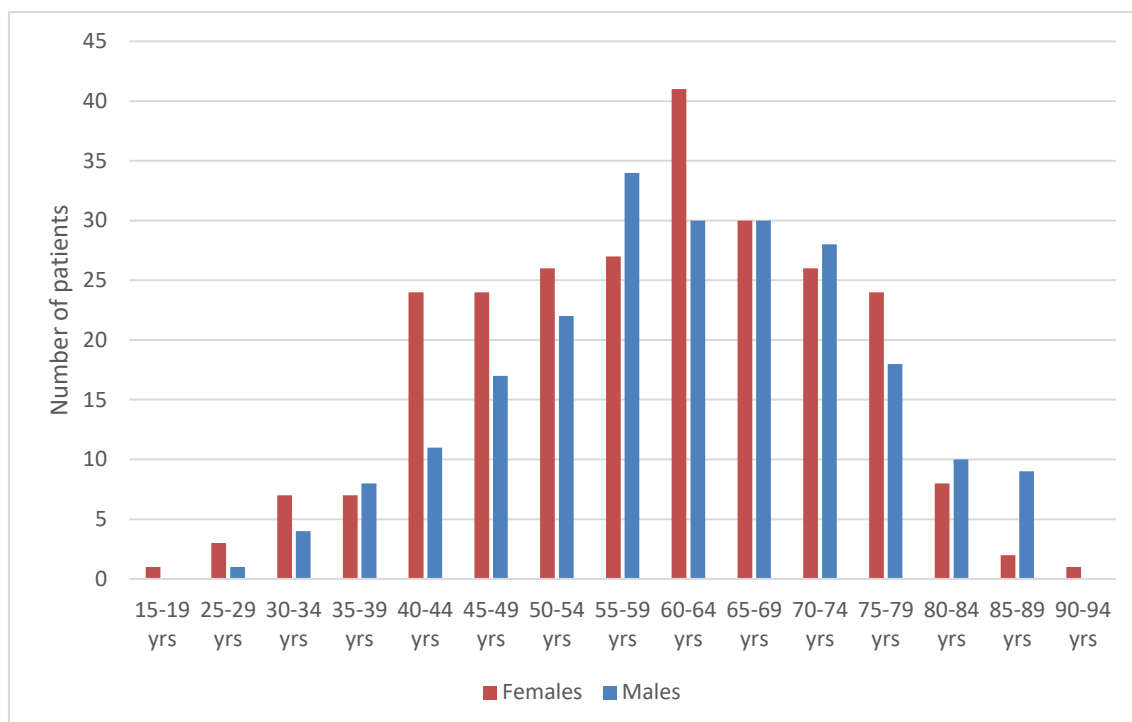


Figure 7: Market share of alectinib and ceritinib according to year

In the submission, the budget impact advisory assessment estimated alectinib would obtain 90% of the second-line ALK-inhibitor market in 2018, and 100% of the market thereafter. This estimate was based on the favourable efficacy and safety profile of alectinib compared to ceritinib and advice from clinicians at a clinical advisory board. Figure 7 meets the submission's estimates well, with the market share of alectinib being approximately 90% in 2018 and approximately 95% thereafter.

Patient level analysis**Figure 8: Age and gender distribution of incident alectinib patients**

From Figure 8, there is a slight positively skewed age distribution in incident alectinib patients, with the most common age group for females and males being 60-64 years and 55-49 years respectively. Overall, the most common age group are those aged between 60-64 years old. In the younger age groups of 54 years and less, females account for a higher ratio of initiating patients than males. In the older age groups, there are varying proportions of female and male patients in each age group.

Table 3: Alectinib study participant versus patient demographics

Baseline characteristic, n (%)	Alectinib study participants			PBS Data (N=473)
	NP28761 (N=87)	NP28673 (N=138)	Pooled data (N=225)	
Age, mean (range)	53.6 (29-79)	51.5 (22-79)	52.3 (22-79)	60 (16-90)
Sex, F	48 (55.2%)	77 (55.8%)	125 (55.6%)	251 (53.1%)

From Table 3, the mean age of alectinib patients are older (60 versus 52.3 years old) with a wider age range (16-90 versus 22-79 years old) compared to the mean age of alectinib study participants. There is a slightly lower proportion of females (53.1%) compared to trial participants (55.6%)

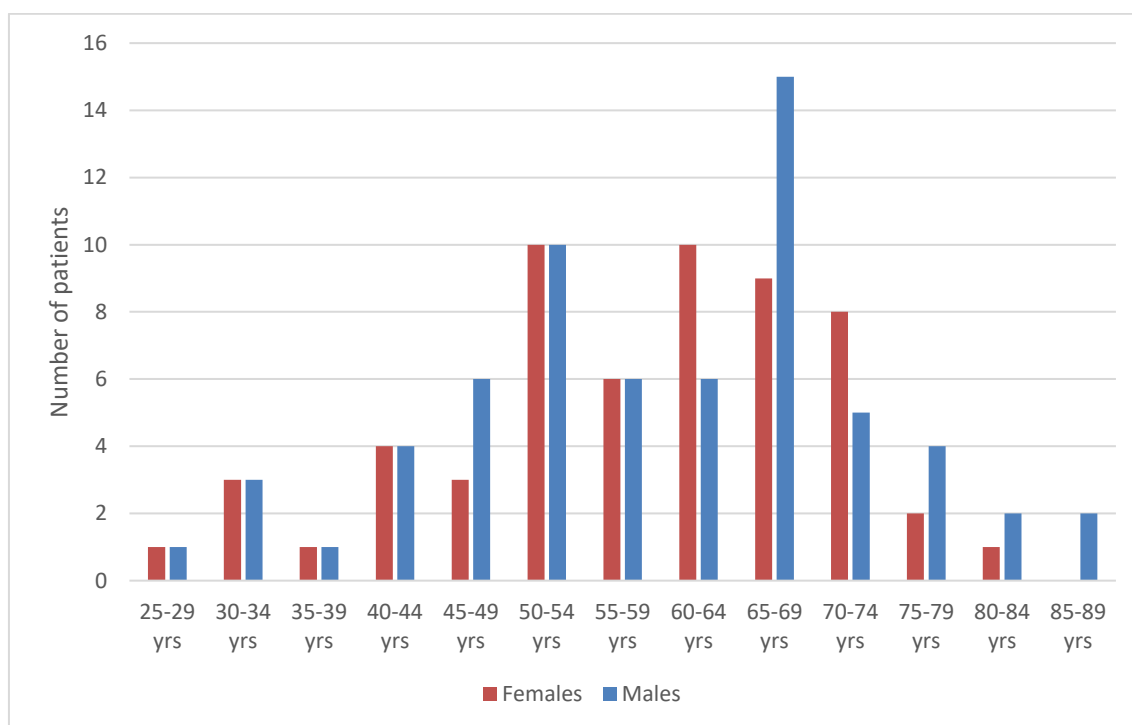


Figure 9: Age and gender distribution of initiating ceritinib patients

From Figure 9, there is a positively skewed age distribution in initiating ceritinib patients. In females, the most common age group are those aged between 50-54 and 60-64 years old. In males, the most common age group are those aged between 65-69 years old. Overall, the most common age group of initiating ceritinib patients are those aged between 65-69 years old. In the younger age groups of 59 years and less, there is a similar ratio of females and males. In the older age groups, there are varying proportions of female and male patients in each age group.

Table 4: Ceritinib study participant versus patient demographics

Baseline characteristic, n (%)	Ceritinib study participants		PBS Data (N= 123)
	ASCEND-1 (N=163)	ASCEND-2 (N=140)	
Age, median (range)	52 (24-80)	51 (29-80)	60 (25-89)
Sex, F	88 (54.0%)	70 (50.0%)	58 (47.2%)

From the table, the median age of ceritinib patients (60 years old) is higher than the median age of trial participants (52 and 51 years old). The youngest initiating patient (25 years old) is similar with those of study participants (24 and 29 years old). An 89 year old was the oldest initiating alectinib patient, being older than study participants (80 years old). A slightly lower proportion of females (47.2%) is observed compared to study participants (54% and 50%).

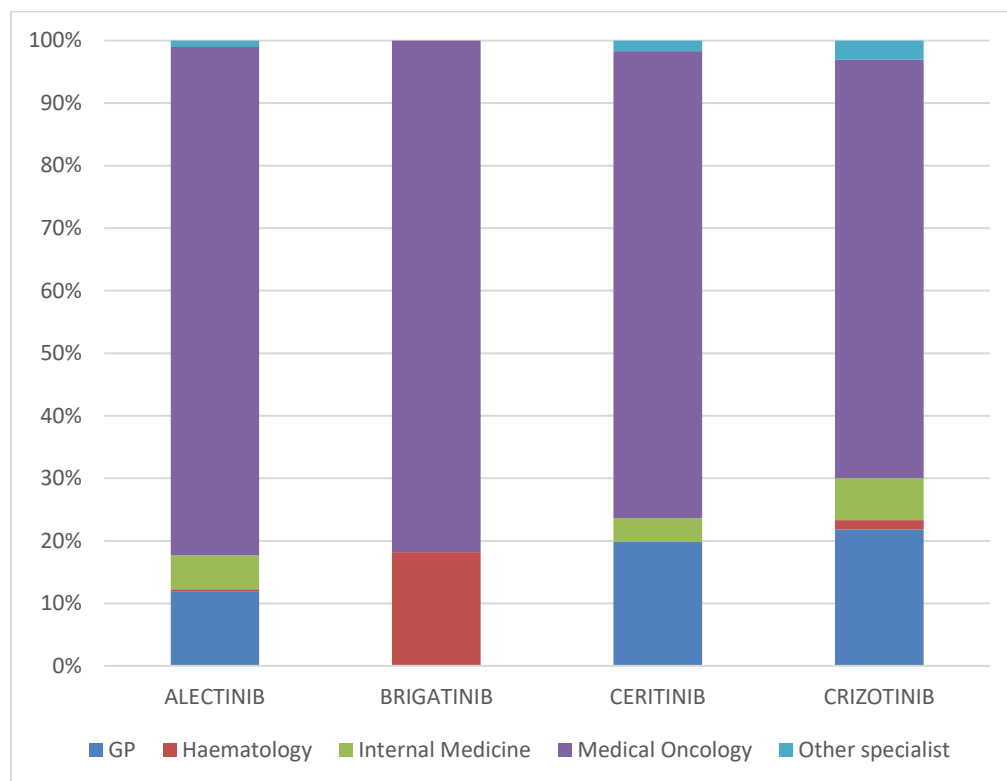


Figure 10: ALK-inhibitor prescribers: alectinib, brigatinib, ceritinib, crizotinib

Note: "Other specialist" defined as including cardiology, clinical genetics, endocrinology, gastroenterology and hepatology, nuclear medicine, paediatric medicine, palliative medicine, pathology, rehabilitation medicine, respiratory and sleep medicine, rheumatology, sexual health medicine specialists and college trainee-physician

Note: "GP" defined as including non-vocationally registered GP, vocationally registered GP, trainee GP and GP with unclassified registration status.

Note: 8.74% of scripts had an unknown prescriber

Oncologists account for the majority ALK-inhibitor prescribers, accounting for at least 50% of prescribers in all four ALK-inhibitors. Internal medicine clinicians account for approximately 5% of prescribers in alectinib, ceritinib and crizotinib. Brigatinib has only been prescribed by oncologists and haematologists. 18% of brigatinib scripts and less than 5% of alectinib and crizotinib scripts were prescribed by haematologists. Similar proportions of alectinib and ceritinib scripts and a slightly higher proportion of crizotinib scripts were prescribed by GPs.

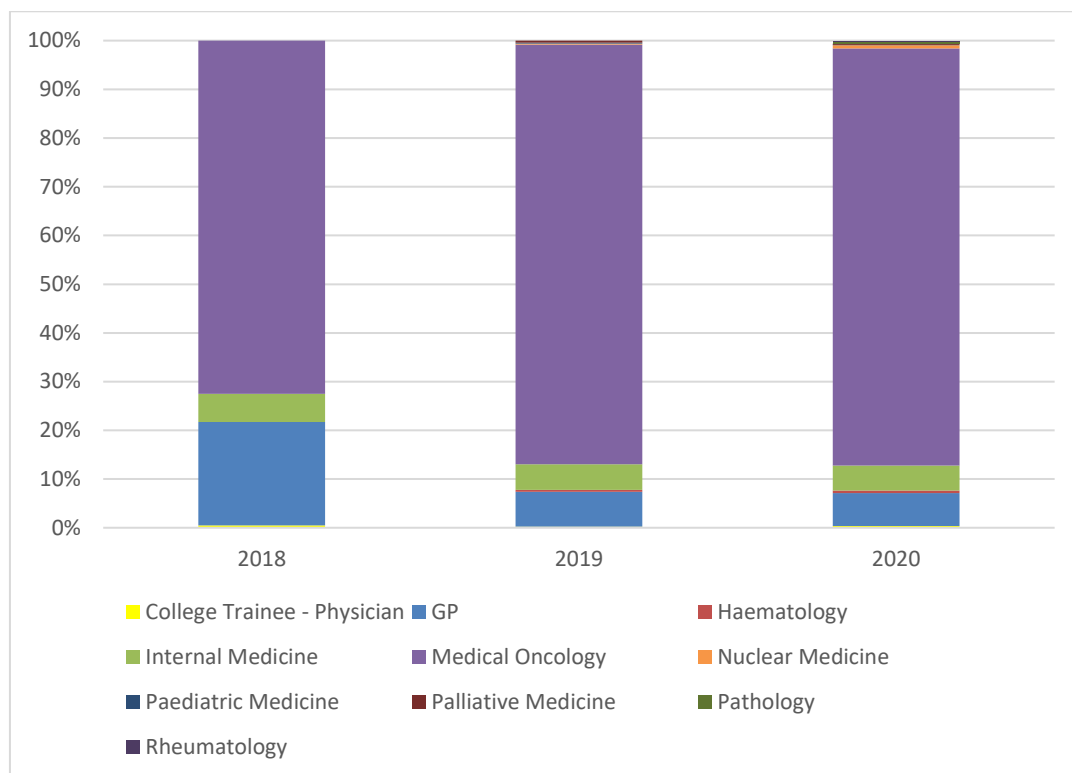


Figure 11: Distribution of alectinib prescribers according to year

Note: "GP" defined as including non-vocationally registered GP, vocationally registered GP, trainee GP and GP with unclassified registration status

Note: The year 2020 only includes six months of data.

From Figure 11, since alectinib was PBS listed there has been an increase in the number of scripts prescribed by oncologists and a decrease in scripts prescribed by GPs. Of alectinib scripts prescribed in 2018, approximately 73% were prescribed by oncologists, 21% were prescribed by GPs and 6% prescribed by internal medicine clinicians with a small proportion prescribed by college trainee physicians. Of alectinib scripts prescribed in 2019, approximately 86% were prescribed by oncologists, 7% were prescribed by GPs, 5% were prescribed by internal medicine clinicians with the remaining prescribed by college trainee physicians, haematology, nuclear medicine, paediatric medicine and palliative medicine specialists. Similar proportions were observed in 2020.

Table 5: ALK-inhibitor switching sequence prior to alectinib PBS listing (from July 2015 to December 2017)

Drug initiation sequence	Number of patients
CRIZOTINIB	98
CRIZOTINIB>CERITINIB	27
CERITINIB	13
CRIZOTINIB>CERITINIB>CRIZOTINIB	<5

Table 5 shows the drug sequence trends before alectinib was PBS listed. From the table, the most common drug sequence was 98 patients who initiated and remained on crizotinib. After ceritinib was PBS listed, 13 patients initiated and remained on ceritinib and 27 patients who initiated on crizotinib switched to ceritinib.

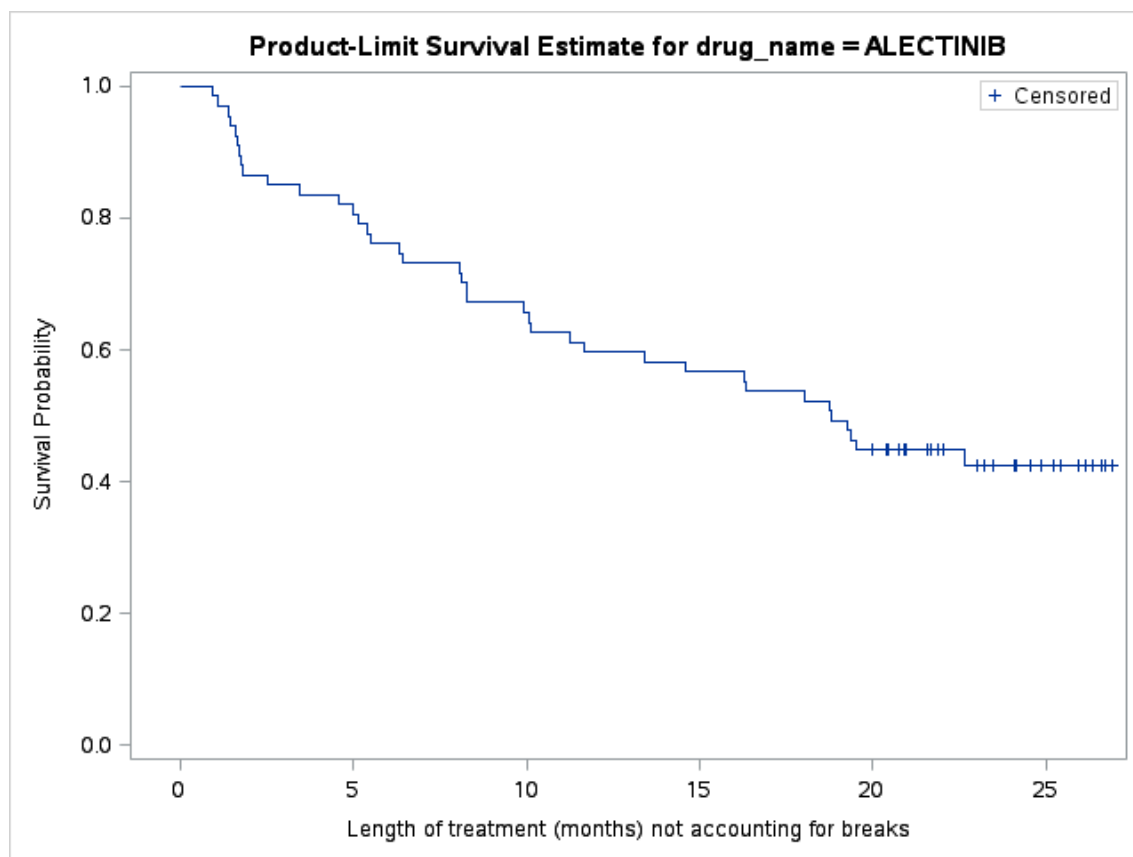
Table 6: ALK-inhibitor switching sequence since crizotinib PBS listing (from July 2015 to June 2020)

Drug initiation sequence	Number of patients
ALECTINIB	297
CRIZOTINIB	144
CRIZOTINIB>ALECTINIB	103
CRIZOTINIB>CERITINIB>ALECTINIB	37
CRIZOTINIB>CERITINIB	33
CERITINIB	21
CERITINIB>ALECTINIB	12
THREE OR MORE SWITCHES	12
ALECTINIB>CERITINIB	8
UP TO TWO SWITCHES AFTER ALECTINIB	≤5
UP TO TWO SWITCHES AFTER CERITINIB	≤5
UP TO TWO SWITCHES AFTER CRIZOTINIB	≤5

From Table 6, the most common drug sequence was 297 patients who initiated and remained on alectinib. 103 patients who switched from crizotinib to alectinib and 37 patients who switched from crizotinib to ceritinib to alectinib, were the third and fourth most common drug sequences respectively. The second most common treatment pathway was 144 patients who initiated and remained on crizotinib. Of patients who initiated on crizotinib and switched to ceritinib, 52% switched to alectinib afterwards. Twelve patients had switched from ceritinib to alectinib and eight patients had switched from alectinib to ceritinib.

Table 7: Estimated length of treatment from Kaplan Meier analysis in patients who began alectinib treatment from 1 April 2018 to 31 October 2018 and followed to 30 June 2020

Number of patients	Censored	Mean (months)	Standard error	95% confidence interval (months)	
				Lower Limit	Upper Limit
67	27	15.29	1.10	13.10	17.48

**Figure 12: Kaplan Meier curve of alectinib treatment duration without accounting for breaks in patients who initiated from 1 April 2018 to 31 October 2018 followed to 30 June 2020.**

The submission noted an independent review committee assessed the mean duration of progression free survival in the pooled analysis of the alectinib NP28761 and NP2873 trials to be 11.64 months. The BIA concluded patients would require 11.64 months of treatment.

Figure 12 shows a Kaplan Meier curve for the duration of alectinib treatment without accounting for breaks. The mean treatment duration of alectinib was 15.29 months (95%CI 13.10-17.48 months). The mean duration of treatment for ceritinib is not presented due to the low number of ceritinib patients.

Table 8: Estimated length of treatment from Kaplan Meier analysis in patients who began alectinib treatment from 1 April 2018 to 31 October 2018 and followed to 30 June 2020, accounting for breaks

Number of patients	Censored	Mean (months)	Standard error	95% confidence interval (months)	
				Lower Limit	Upper Limit
67	1	13.78	1.02	11.75	15.80

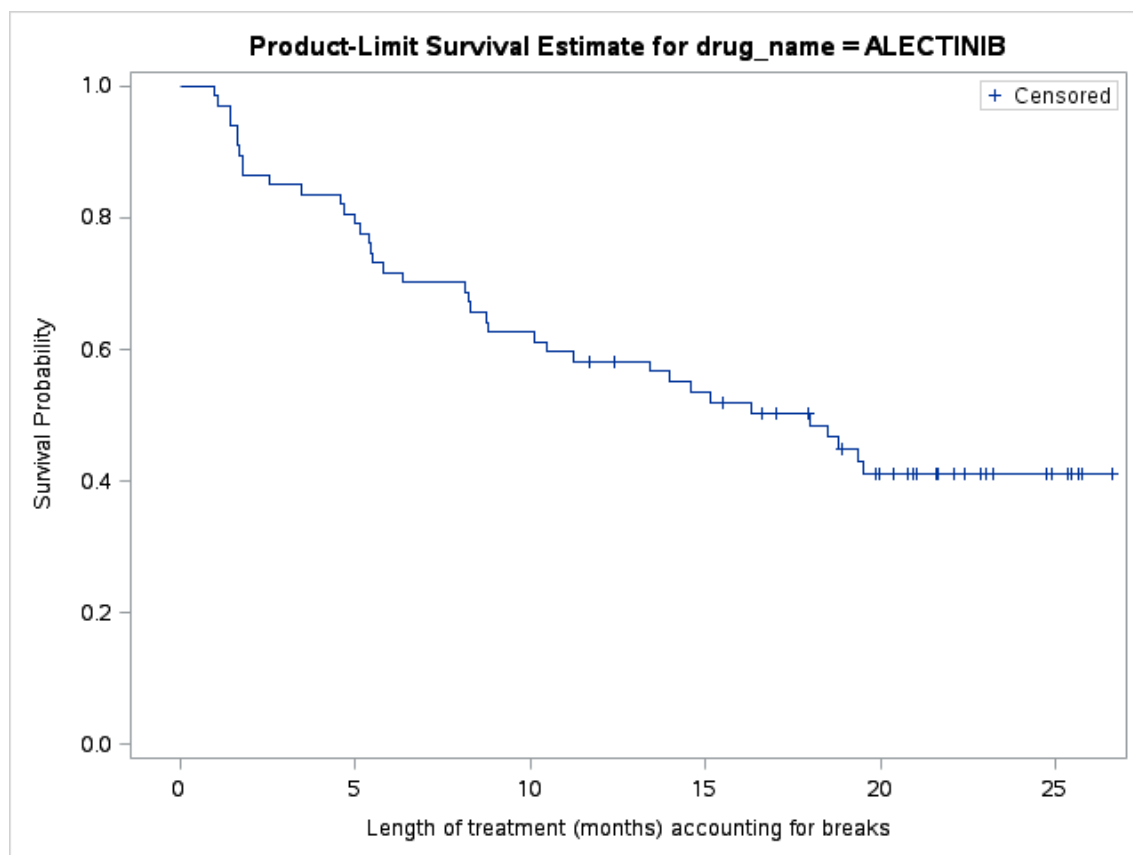


Figure 13: Kaplan Meier curve of alectinib treatment duration accounting for breaks in patients who initiated from 1 April 2018 to 31 October 2018 followed to 30 June 2020.

Figure 13 shows that when accounting for treatment breaks, the mean treatment duration of alectinib was 13.78 months (95%CI 11.75-15.80 months) accounting for breaks.

Analysis of actual versus predicted utilisation

Table 9: Alectinib actual versus predicted utilisation

Alectinib listing years		Year 1	Year 2	Year 3
		January 2018- December 2018	January 2019 - December 2019	January 2020- December 2020
Patients	Predicted	161	147	150
	Actual	254	322	306
	Difference	+58%	+119%	+104%
Prescriptions	Predicted	780	792	804
	Actual	1,715	2,546	1,501
	Difference	+120%	+221%	+87%

Note: The predicted number of treated patients in the first year of listing includes 30 grandfathered patients. Year 3 predicted numbers are for the full year, actual numbers are six months of data.

From Table 9, actual patient and prescription figures were higher than estimated. The number of patients in the first and second year of alectinib listing was greater by 58% and 119%, respectively. Despite Year 3's actual figures only being for six months of data, it is already twice than estimated for the full year (+104%).

In terms of prescription numbers, the number of alectinib prescriptions dispensed in its first year of listing was more than double (+121%) the estimated number. In its second year, actual prescription numbers were 221% greater than estimated. In Year 3 with only six months of data, there is already an 87% difference compared to the estimated prescription numbers for the full year.

The table shows a greater increase in the estimated number of prescriptions (+120%, +221%, +87%) compared to the number of patients (+58%, +119%, +104%). Therefore, alectinib patients are dispensed more prescriptions or staying longer on treatment than estimated.

Table 10: Predicted versus actual number of doses (capsules) required per course of alectinib treatment

	Predicted	Actual	Difference
Strength (mg)	150	150	-
Daily dose	1,200	1,200	-
Duration of treatment (weeks)	50.5	59.9	+19%
Doses (capsules)/treatment	2,829	3,354	+ 19%

Note: Adapted from '3a. Volumes - new' Tab of Section 4 Workbook from the BIA.

"Strength (mg)" and "Daily dose" values from TGA Product Information.

"Duration of treatment" estimate from mean duration of progression-free survival by independent reported in pooled analysis trials NP28761 and NP28763 (alectinib).

"Doses (capsules)/treatment" calculated by (daily dose / strength (mg))*(duration of treatment (weeks)*7)

From Table 10, the submission estimated based on the duration of treatment of 50.5 weeks, 2,829 doses (capsules) would be required per course of alectinib treatment and 1,768 doses (capsules) would be required per course of ceritinib treatment.

Based on the mean duration of treatment calculated in Figure 13 of 13.78 months (equivalent to 59.9 weeks), 3,354 doses (capsules) are dispensed per course of alectinib treatment. This is higher than estimated due to the longer duration of treatment in practice.

Table 11: Predicted versus actual scripts per course of alectinib treatment

	Form/strength	Pack size	Doses/treatment	Scripts/treatment
Predicted	Capsules/ 150 mg	224	2,829	12.63
Actual	Capsules/ 150 mg	224	3,354	14.97

Note: Adapted from '3a. Volumes - new' Tab of Section 4 Workbook.

Using values from Table 10, the submission estimated 12.63 scripts would be dispensed per course of alectinib treatment. Based on 3,354 doses per course of treatment calculated in Table 9, 16.48 scripts were dispensed per course of alectinib treatment.

Discussion

Overall, alectinib has quickly established its position in Australia's ALK-inhibitor market. Since its first PBS listing in January 2018, alectinib has increased its market share from 45% to approximately 90% in the second supply quarter of 2020. The increased market share of alectinib has translated to higher than estimated patient and script numbers.

In 2018, patient numbers were 58% higher than estimated and the number of prescriptions were 120% higher than estimated. In 2019, patient numbers were 119% higher than estimated and the number of prescriptions were 221% higher than estimated. Although there was only six months of data available for third year of listing for alectinib, higher than predicted numbers were already discerned with patient numbers 104% higher and script numbers 87% higher than estimated. Overall, there was a greater percentage increase in the number of prescriptions dispensed compared to the number of patients. This could be attributed to patients being dispensed more scripts or patients remaining on treatment for longer.

As predicted in the submission, the mean treatment duration of alectinib of 13.78 months (95%CI 11.75-15.80 months) or 59.9 weeks was longer than calculated in trial data. The submission estimated that the duration of a course of alectinib would be 11.64 months or 50.5 weeks. The submission mentioned the majority of study participants had prior treatment of crizotinib and chemotherapy and would require less doses to inhibit ALK activity. Therefore, the longer than estimated treatment duration has led to an increase in the number of doses and subsequently the number of prescriptions dispensed per treatment regimen. A study by Mok et al. (2020) with 38 months of follow up, reported a

median treatment duration of 28.1 months and a median PFS of 34.8 months.¹¹ The duration of response was longer compared to other ALK-inhibitors. The CNS penetration of three year PFS was 40.5% compared to 2.1% for crizotinib.

Higher than estimated utilisation rates could be attributed to a number of reasons, including alectinib having potentially less toxicity. Recent systematic reviews have demonstrated that alectinib may have increased progression free survival compared to other ALK-inhibitors and greater management of CNS metastases.^{12,13}

As shown in Figure 3, the number of patients receiving ALK-inhibitor treatment has grown from 184 patients (prior to the PBS listing of alectinib, fourth quarter of 2017) to 330 patients (second quarter of 2020). From Table 5, most patients on ALK-inhibitor treatment were those who initiated with and remained on crizotinib treatment, prior to alectinib being PBS listed. In Table 6, most patients on ALK-inhibitor therapy have initiated and remained on alectinib treatment once alectinib was PBS listed. The second most common pathway were patients who commenced and remained on crizotinib treatment. The third and fourth most common sequences were patients who switched from crizotinib to alectinib and patients who switched from crizotinib to ceritinib to alectinib.

Overall, of patients currently treated with alectinib, those who commenced ALK therapy with alectinib accounted for a greater proportion compared to those switching from ceritinib or crizotinib. As alectinib was PBS listed as line agnostic without any restriction to line of therapy, clinicians or patients were inclined to use alectinib as a first line treatment option instead of ceritinib or crizotinib.

A low number of patients were supplied ceritinib. Due to these low numbers, this has resulted in limited analysis of the duration of ceritinib treatment and the mean scripts per patient and subsequently the script substitution rate of alectinib for ceritinib.

DUSC consideration

DUSC noted as alectinib was PBS listed as line agnostic, clinicians or patients were inclined to use alectinib as a first line treatment option instead of ceritinib or crizotinib. DUSC noted the switching analysis demonstrated patients were most commonly treated with alectinib alone or switched from other ALK- inhibitors to alectinib.

¹¹ Mok T, Camidge D R, Gadgeel S M, Rosell R, Kim D.-W, Perol M, et al. Updated overall survival and final progression-free survival data for patients with treatment-naïve advanced ALK-positive non-small-cell lung cancer in the ALEX study. *Annals of Oncology*. 2020 Aug. 31 (8) Available from: <https://doi.org/10.1016/j.annonc.2020.04.478>

¹² Elliott J, Bai Z, Hsieh S-C, et al. ALK inhibitors for non-small cell lung cancer: A systematic review and network meta-analysis. *PLoS ONE* 2020; 15 (2):e0229179

¹³ Yang YL, Xiang ZJ, Yang JH, Wang WJ, Xiang RL. Effect of alectinib versus crizotinib on progression-free survival, central nervous system efficacy and adverse events in ALK-positive non-small cell lung cancer: a systematic review and meta-analysis. *Ann Palliat Med*. 2020;9(4):1782-1796. doi:10.21037/apm-19-643

DUSC noted alectinib quickly established its position in the ALK-inhibitor market with its market share increasing from 45% in quarter 1 2018 to 90% in 2020. This has translated to higher than predicted patient and script numbers. DUSC considered the submission's estimates were relatively accurate in terms of the market share of alectinib and ceritinib.

DUSC noted that the mean treatment duration was 15.3 months not accounting for breaks and was 13.8 months accounting for breaks which was longer than estimates based on the clinical trials. DUSC noted the Mok et al. (2020) study with 38 months of follow up, reported a median treatment duration of 28.1 months and a median PFS of 34.8 months. The duration of response was longer compared to other ALK-inhibitors. DUSC considered, despite multiple drugs marketed in the ALK-inhibitor class, alectinib appears to be preferred due to its efficacy. DUSC noted the CNS penetration of three year PFS for alectinib was 40.5% compared to 2.1% for crizotinib.

DUSC commented all Phase 3 studies for alectinib were conducted in Asian populations, where it may be difficult to translate the findings to a Caucasian population. Whereas Phase 3 studies for brigatinib were performed across the US, Europe and Asia, but with a shorter duration of follow-up compared to alectinib.

DUSC actions

DUSC requested that the report be provided to the PBAC for consideration.

Context for analysis

The DUSC is a Sub Committee of the Pharmaceutical Benefits Advisory Committee (PBAC). The DUSC assesses estimates on projected usage and financial cost of medicines.

The DUSC also analyses data on actual use of medicines, including the utilisation of PBS listed medicines, and provides advice to the PBAC on these matters. This may include outlining how the current utilisation of PBS medicines compares with the use as recommended by the PBAC.

The DUSC operates in accordance with the quality use of medicines objective of the National Medicines Policy and considers that the DUSC utilisation analyses will assist consumers and health professionals to better understand the costs, benefits and risks of medicines.

The utilisation analysis report was provided to the pharmaceutical sponsors of each drug and comments on the report were provided to DUSC prior to its consideration of the analysis.

Sponsor's comment

Roche Products Pty Ltd: The sponsor has no comment

Disclaimer

The information provided in this report does not constitute medical advice and is not intended to take the place of professional medical advice or care. It is not intended to define what constitutes reasonable, appropriate or best care for any individual for any given health issue. The information should not be used as a substitute for the judgement and skill of a medical practitioner.

The Department of Health (DoH) has made all reasonable efforts to ensure that information provided in this report is accurate. The information provided in this report was up-to-date when it was considered by the Drug Utilisation Sub-committee of the Pharmaceutical Benefits Advisory Committee. The context for that information may have changed since publication.

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