Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Alectinib

Proprietary Product Name: Alecensa

Sponsor: Roche Australia Pty Ltd

March 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
BID	Twice daily
C-DOR	CNS duration of response
C-ORR	CNS objective response rate
C-PR	CNS progression rate
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DOT	Duration of treatment
ECOG PS	Eastern cooperative oncology group performance status
eGFR	Estimated glomerular filtration rate
EGFR	Epidermal growth factor receptor
EORTC	European Organization for the Research and Treatment of Cancer
FDA	U.S. Food and Drug Administration
FISH	Fluorescence in situ hybridization
FSH	Follicle-stimulating hormone
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
HR	Hazard ratio
HRQoL	Health-related quality of life
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry

Abbreviation	Meaning
ILD	Interstitial lung disease
IRB	Institutional review board
IRC	Independent review committee
ITT	Intent-to-treat
KRAS	Kirsten rat sarcoma viral oncogene homolog
MET	Mesenchymal-epithelial transition factor
MRI	Magnetic resonance imaging
NSCLC	Non–small cell lung cancer
ORR	Objective response rate
OS	Overall survival
P-gp	P-glycoprotein
PD	Progressive disease
PFS	Progression-free survival
PK	Pharmacokinetic
PS	Performance status
QLQ-C30	Quality of Life Questionnaire–Core
QLQ-LC13	Quality of Life Questionnaire lung cancer module
QTcF	QT interval corrected using Fridericia's formula
RANO	Revised Assessment in Neuro Oncology
RCR	Roche clinical repository
RECIST	Response Evaluation Criteria in Solid Tumors
ROS1	C-ros oncogene 1
SAE	Serious adverse event

I. Introduction to product submission

Submission details

Type of submission:	Extension of Indications
Decision:	Approved
Date of decision:	30 January 2018
Date of entry onto ARTG	30 January 2018
Active ingredient(s):	Alectinib
Product name(s):	Alecensa
Sponsor's name and address:	Roche Australia Pty Ltd 30-34 Hickson Road, Sydney NSW 2000
Dose form(s):	Hard capsule
Strength(s):	150 mg
Container(s):	Blister pack
Pack size(s):	8 capsules per blister pack. Each Alecensa multipack contains 224 (4 packs of 56) capsules.
Approved therapeutic use:	*Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC).*
Route(s) of administration:	Oral (PO)
Dosage:	The recommended dose of Alecensa is 600 mg (four 150 mg capsules) given orally, twice daily with food (total daily dose of 1200 mg).
ARTG number (s):	272115

Product background

This AusPAR describes the Priority review application by Roche Australia Pty Ltd to extend the indications of Alecensa (containing 150 mg (dry weight) alectinib) to also include first line treatment for the same patient group. The sponsor proposes the following new wording for the indications:

> *Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC).*

The currently approved indication in Australia is as follows:

> *Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.*
> *Note to Indication: This indication is approved based on tumour response rates and*

duration of response. An improvement in survival or disease-related symptoms has not been established.

The proposed dosage is 600 mg (four 150 mg capsules) given orally, twice daily with food (total daily dose of 1200 mg) and is unchanged from the previous approval.

This application includes Study BO28984 (ALEX), the confirmatory Phase III clinical trial for the initial registration on early data and its submission meets one of the conditions of the initial TGA registration.

The ALEX trial is a confirmatory Phase III trial in which alectinib was compared head-to-head against crizotinib in first line usage: in subjects who had no previous systemic therapy (approximately 8% had previous neoadjuvant systemic therapy). On the basis of the results from the ALEX trial, the current submission proposes removal of the restriction to later than first-line use, as well as removal of the note to the current indication regarding the limitations of the available efficacy dataset at the time of initial approval[1].

Alectinib is a tyrosine kinase inhibitor that targets anaplastic lymphoma kinase (ALK) and Rearranged during Transfection (RET) tyrosine kinase. In nonclinical studies, alectinib inhibits ALK tyrosine kinase activity, leading to blockage of downstream signalling pathways including Signal transducer and activator of transcription 3 (STAT3) and phosphoinositide 3-kinase (PI3K)/ protein kinase B (PKB or AKT) and inhibits proliferation of cancer cells harbouring ALK fusion proteins.

ALK was first identified as a fusion protein resulting from chromosomal translocation in the majority of anaplastic large cell lymphoma (ALCL). When fused to other proteins, ALK becomes constitutively active, leading to increased catalytic kinase function, signal transduction activity and oncogenic function. ALK gene rearrangement is found in about 5% of patients with non−small cell lung cancer (NSCLC)[2] and is thought to be mutually exclusive with epidermal growth factor receptor (EGFR) and Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations.[3] It has been associated with a younger age, non-smoking status and adenocarcinoma histology and a more advanced state at presentation.[4] In particular, there is a high lifetime risk of brain metastases and in a study of twenty-one newly diagnosed patients, 23.8% were reported to have brain metastases at presentation with a cumulative incidence of post-baseline brain metastases of 45.5% at 2 years and 58.4% after 3 years of survival with the use of targeted therapies.[5] Thus ALK gene rearrangements define a unique molecular subset of NSCLC[2] and effective means of preventing or treating central relapse is an area of unmet need.

The prevalence of ALK-positive lung cancer in Australia was estimated to be approximately 1200 in 2015.

This is the fourth submission for Alecensa received by the TGA, with three other submissions approved by the TGA including the initial registration of the new chemical entity (PM 2015-04677-1-4), a Category 3 application and a safety-related (9D3) request.

[1] Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established.
[2] Shaw AT, Kim DW, Nakagawa K et al (2013). Crizotinib versus Chemotherapy in Advanced ALK-positive Lung Cancer. New England Journal Medicine 368:2385-2394
[3] Gainor JF, Varghese AM, Ou SH, Kabraji S et al (2013). ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. Clin Cancer Res. 2013 Aug 1;19(15):4273-81
[4] Shaw AT, Yeap BY, Mino-Kenudson M, Digumarthy SR, Costa DB et al (2009). Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol. 2009 Sep 10; 27(26):4247-53.
[5] Rangachari D, Yamaguchi N, VanderLaan PA, Folch E et al. (2015). Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. Lung Cancer. Apr;88(1):108-11

Regulatory status

Alectinib was first approved in Australia as a new active substance in March 2017 on the basis of overall response rate (ORR) and duration of response (DOR) results, as well as evidence of efficacy in the central nervous system (CNS), from two single-arm Phase I/II studies (NP28761 and NP28673).

Its indication was restricted to use in patients after crizotinib, which is registered in Australia for the treatment of ALK-positive NSCLC but is not retained in the CNS which is the most common site of disease progression on crizotinib therapy.

FDA

In November 2017, alectinib was approved by the US FDA for first-line treatment of ALK-positive metastatic NSCLC. The FDA has also converted alectinib's accelerated approval for patients with ALK-positive NSCLC who have progressed on crizotinib to a full approval.

The approved US indication is now:

> *ALECENSA is a kinase inhibitor indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA- approved test.*

European Medicines Agency (EMA)

On 12 October 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorisation for the medicinal product Alecensa. The marketing authorisation holder for this medicinal product is Roche Registration Limited.

The CHMP adopted an extension to the existing indication as follows[1]:

> *Alecensa as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC).*
>
> *Alecensa as monotherapy is indicated for the treatment of adult patients with ~~anaplastic~~ ~~lymphoma kinase (ALK)~~ -positive advanced ~~non-small cell lung cancer~~ ~~(~~NSCLC) previously treated with crizotinib.*

In addition, since all specific obligations of the conditional marketing authorisation have been fulfilled, the marketing authorisation for Alecensa will be switched from conditional to full approval.

On the 18 December 2017, the European Commission (EC) approved Alecensa as a monotherapy for the first-line treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive, advanced non-small cell lung cancer (NSCLC). In addition to the first-line approval, the EC also converted the conditional marketing authorisation of Alecensa in crizotinib failure to a standard marketing authorisation.

The following table summarises the international regulatory status of Alecensa.

Table 1: Summary table of overseas regulatory status for the current submission (at 9 January 2018)

Jurisdiction	FDA	EMA
Approval date	November 2017	December 2017
Indication	ALECENSA is a kinase inhibitor indicated for the treatment of patients	Alecensa as monotherapy is indicated for the first-line treatment of adult patients with anaplastic lymphoma

Jurisdiction	FDA	EMA
	with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) as detected by an FDA-approved test.	kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC). Alecensa as monotherapy is indicated for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib.

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Currently, the only approved first line therapy for ALK-positive NSCLC is either crizotinib or chemotherapy. There is a strong, unmet clinical need for improvement upon the gains made in the treatment of advanced ALK-positive NSCLC with the use of crizotinib, and in particular, for better ways to treat the brain metastases that are either present at baseline or develop during crizotinib treatment. The current submission includes a pivotal study of patients with ALK-positive NSCLC not previously treated with systemic therapy for advanced or metastatic disease randomised to receive either alectinib or crizotinib, the current standard of care. This study assesses the effect of alectinib on PFS with a particular focus on the CNS efficacy in those with brain or developing metastases, and provides data to support the use of a companion diagnostic assay for alectinib (Ventana IHC), noting the current requirement for access in Australia is a FISH test following initial detection by immunohistochemistry (IHC).

First generation ALK inhibitor Crizotinib

ALK gene rearrangements were identified as an oncogenic driver in this subset of NSCLC and this potential target has been confirmed by the improvement in response rates and progression free survival with crizotinib. This non-specific small molecule ALK, cMET and c-ros oncogene 1 (ROS-1) inhibitor is the only targeted agent currently approved for first-

line treatment of locally advanced or metastatic ALK-positive NSCLC. Phase III trials in patients who had received one prior line of chemotherapy demonstrated a response rate of 65% (95% CI: 58, 72) for crizotinib compared with 20% (95% CI: 14, 26) with chemotherapy (P<0.001). The median progression free survival (PFS) was 7.7 months compared with 3.0 months in patients who received single-agent chemotherapy (Hazard ratio 0.49; 95% confidence interval (CI): 0.37, 0.64; p<0.001). Improvement in OS was not demonstrated and crossover to crizotinib on progression in the chemotherapy arm is likely to account for this. This study also includes one of the first reports of chemotherapy response rates in ALK-positive NSCLC (compared with NSCLC not otherwise specified). This trial followed single-arm trials of crizotinib in patients with ALK-positive NSCLC where response rates of 50 to 61% and duration of response of 6 to 10 months were reported.[6] In a Phase III open label trial in the first line setting, crizotinib resulted in a significantly increased median PFS compared with pemetrexed and platinum doublet chemotherapy of 10.9 months versus 7.0 months, HR 0.45; 95% CI:0.35, 0.6, p<0.001). Quality of life and symptom control were also reported to be improved with crizotinib.[7] This confirmed the standard of care to be crizotinib in patients newly diagnosed with locally advanced or metastatic ALK-positive NSCLC.

Crizotinib is currently the only TGA approved targeted therapy for ALK-positive NSCLC for use in previously untreated patients:

Crizotinib (Xalkori) is registered by the TGA for the treatment of patients with ALK-positive advanced non-small cell lung cancer.

Acquired resistance and brain metastases

Acquired drug resistance to crizotinib remains a problem and may result from the development of resistant ALK mutations, ALK amplification and/or activation of alternate aberrant signalling pathways.[8] Crizotinib does not cross the blood-brain barrier efficiently, resulting in low levels in the cerebrospinal fluid and limited CNS activity[5] but the results presented in this application do indicate an overall CNS response rate in the crizotinib arm. Brain metastases are common in NSCLC and often the first site of progression on crizotinib. Therefore, effective management of brain metastases remains an issue in this disease.

Furthermore, not all patients respond to, or tolerate crizotinib treatment. Crizotinib has the following significant toxicities: hepatotoxicity (including fatal cases), pneumonitis (including fatal cases), QT prolongation[9], bradycardia (usually asymptomatic) and vision disorders. A more recent signal of renal toxicity has been detected.

[6] Ou SH (2011). Crizotinib: a novel and first-in-class multitargeted tyrosine kinase inhibitor for the treatment of anaplastic lymphoma kinase rearranged non-small cell lung cancer and beyond. Drug Des Devel Ther. 2011;5:471-85.

[7] Solomon, B et al, First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. N Engl J Med 2014; 371:2167-2177

Costa CB, Kobayashi S, Pandya SS (2011). Concentration of the anaplastic lymphoma kinase inhibitor crizotinib. J Clin Oncol 29:e443-5

[8] Doebele RC, Pilling AB, Aisner DL, et al. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non−small cell lung cancer. Clin Cancer Res 2012; 18:1472.

Katayama R, Khan TM, Benes C, et al. Therapeutic strategies to overcome crizotinib resistance in non−small cell lung cancers harboring the fusion oncogene EML4-ALK. Proc Natl Acad Sci USA 2011;108:7535.

[9]The QT interval is the time from the start of the Q wave to the end of the T wave. It represents the time taken for ventricular depolarisation and repolarisation, effectively the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation. The QT shortens at faster heart rates. An abnormally prolonged QT is associated with an increased risk of ventricular arrhythmias, especially Torsades de Pointes. The recently described congenital short QT syndrome has been found to be associated with an increased risk of paroxysmal atrial and ventricular fibrillation and sudden cardiac death.

Second-generation ALK inhibitors

Second generation ALK inhibitors registered by the TGA include ceritinib and alectinib and these are discussed further below. Both were given approval on single arm Phase II studies on the basis of response rates in those previously treated with crizotinib (either with disease progression or intolerance) and the notes to the indication identify the preliminary nature of the data supporting the findings in these submissions in this uncommon cancer.

Alectinib

Alectinib is currently approved in Australia for the following indication:

> *Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.*
>
> *Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease-related symptoms has not been established*.

Alectinib is reported to be a selective and potent oral next generation lipophilic ALK inhibitor that is not a P-glycoprotein (P-gp) substrate. Thus, it is able to penetrate the blood-brain barrier and has the potential to reach higher concentrations in the brain as compared to substrates of P-gp such as crizotinib.

In patients with crizotinib-refractory ALK-positive NSCLC treated with alectinib in a Phase II study, the CNS objective response rate in 35 patients with baseline measurable CNS lesions was 57% (95% CI, 39% to 74%).[10] In a pooled analysis from two Phase II studies, alectinib demonstrated significant disease activity in patients previously treated with crizotinib with brain metastases (some patients had also received prior CNS radiation).[11]

Use in patients with Study AF-001JP, assessing alectinib in patients with ALK-positive NSCLC who are crizotinib-naive and have disease progression after at least one line of chemotherapy, reported that the median treatment duration in the study had not been achieved as 86% of patients were still active on the study but the projected median duration of therapy is estimated to be at least 14 months at the final point of data collection.[12]

The clinical development program for alectinib in first-line NSCLC comprises three Phase III studies: JO28928 (J-ALEX), ALEX and YO29449 (ALESIA). J-ALEX was a study conducted only in Japan and led by the co-development partner with a dose of 300 mg twice daily (BID).[13] The ALESIA study was initiated in June 2016 and is currently ongoing to evaluate the efficacy and safety of alectinib 600 mg BID versus crizotinib 250 mg BID and to evaluate the PK of alectinib in Asian patients with treatment-naive ALK-positive advanced NSCLC.

In a first-line head-to-head study of 207 Japanese patients with ALK-positive NSCLC randomly assigned to crizotinib or alectinib, at a planned interim analysis, results

[10] Ou SH, Ahn JS, De Petris L, Govindan R, Yang JC et al (2016). Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. J Clin Oncol. 2016 Mar 1; 34(7):661-8.
[11]Gadgeel SM, Shaw AT, Govindan R, Gandhi L, Socinski MA and Camidge RA (2016). Pooled Analysis of CNS Response to Alectinib in Two Studies of Pretreated Patients With ALK-Positive Non–Small-Cell Lung Cancer. J Clin Oncol 34: 4079-4085
[12] Inoue A, Kobayashi K, Maemondo M, Sugawara S, Oizumi S et al (2013). Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations. Ann Oncol. 2013 Jan; 24(1):54-9.
[13] Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, Takiguchi Y et al (2017). Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. Lancet. 2017 Jul 1; 390(10089):29-39.

demonstrated improved PFS with alectinib (median PFS was not reached in the alectinib arm and was 10.2 months in the crizotinib arm (hazard ratio [HR] 0.34, 99.7% CI 0.17-0.70)).[13] The current submission includes the study report for the larger Phase III global study of 303 patients randomly assigned to first-line *alectinib* versus crizotinib (ALEX), with the published results reported to indicate superior efficacy (including CNS activity) and safety for alectinib in comparison with crizotinib.[14]

This application meets the registration condition of submission of the confirmatory Phase III study in those not previously treated for metastatic ALK-positive NSCLC, randomised either to receive alectinib or crizotinib. On the basis of very promising PFS data, the TGA has given alectinib priority review designation.

Note is made that both the EMA and FDA have received the data from the J-ALEX study for evaluation as part of the review for the first line indication application, but this has not been submitted to the TGA as part of the current application.

Ceritinib

Ceritinib is an oral medicine and is stated to be a potent inhibitor of ALK kinase, with activity against ALK-positive NSCLC that has developed resistance to crizotinib. It was approved by the TGA on 24 March 2016 for the following indication:

> *Zykadia is indicated as monotherapy for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive locally advanced or metastatic non-small cell lung cancer (NSCLC) whose disease has progressed on or who are intolerant of crizotinib.*
>
> *Note to Indication: This indication is approved based on tumour response rates and duration of response. An improvement in survival or disease –related symptoms has not been established.*

A recent Phase III study comparing ceritinib as first line treatment comparing with platinum-doublet chemotherapy in those with metastatic or unresectable ALK-positive NSCLC was published recently[15] and led to the approval for use in the first line setting in the EMA and FDA in 2017. This places ceritinib as a potential alternative to chemotherapy and crizotinib. Ceritinib has significant toxicities including hepatotoxicity, gastrointestinal (GI) toxicity and QT prolongation as well as potential for deleterious drug interactions.

Brigatinib and lorlatinib are other ALK inhibitors but neither is currently approved for use in Australia. Brigatinib was approved in the USA (28 April 2017) and lorlatinib had not been approved in the US or EU at the time of writing this report.

Other therapies post-targeted therapy

After exhausting all ALK targeted therapies, patients may be treated with chemotherapy or with immunotherapy, with pembrolizumab, atezolizumab and nivolumab approved for the treatment of patients with ALK-positive NSCLC that has been previously treated with targeted therapy. Other palliative treatment modalities include radiation therapy, and where appropriate, surgery.

Evaluator's commentary on the background information

Alectinib has already demonstrated efficacy in previously treated patients with ALK-positive NSCLC, including those with brain metastases, and this randomized controlled Phase III trial comparing alectinib with crizotinib will help determine the standard of care

[14] Peters S, Camidge R, Shaw AT, Gadgeel S et al (2017). Alectinib versus Crizotinib in Untreated ALK-Positive Non–Small-Cell Lung Cancer. N Engl J Med 2017; 377:829-838

[15] Soria et al (2017). First-line ceritinib versus platinum-based chemotherapy in advanced ALK-rearranged non-small-cell lung cancer (ASCEND-4): a randomized, open-label, phase 3 study. Lancet 389: 917–29 9.

for patients who are newly diagnosed with locally advanced or metastatic disease. Note is made that the website UpToDate, co-authored by Drs Alice Shaw and Ben Solomon, recommends alectinib for use for the first line treatment of locally advanced or metastatic ALK-positive NSCLC.

Guidance

- FDA Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, October 2005.

See also Attachment 2 Guidance for published articles used during this evaluation.

Contents of the clinical dossier

This dossier included:

- Phase III BO28984 'ALEX' randomised controlled open label trial comparing alectinib with crizotinib in patients with treatment-naïve NSCLC.
- Population PK report (1080486) based on the BO28984 (ALEX) population.

The dossier includes the global 'ALEX' study but note is made that the EMA and FDA have both received the 'J-ALEX' conducted exclusively in Japanese patients using the lower dose approved in Japan of 300mg BID. The evaluator has requested safety data from the J-ALEX study where considered relevant.

Within the data package itself, some of the fundamental baseline information required to evaluate the balance between the arms was not presented clearly and narratives for significant adverse events do not appear to have been included.

No overseas reports were provided as this application had not been approved elsewhere at the time of submission and the FDA approved the supplemental new drug application (sNDA) on 6 November 2017.

Paediatric data

No paediatric data were submitted consistent with this being a disease primarily diagnosed in adults.

Good clinical practice

The sponsor states in the Clinical Overview '*The ALEX study was conducted in accordance with Good Clinical Practice (GCP) guidelines. The appropriate Ethics Committees and Institutional Review Boards reviewed and approved this study*.'

Audits were conducted by Roche at three investigator sites. No critical or major finding(s) involving non-compliance with GCP were observed in any of these audits. Appropriate corrective and preventive actions were undertaken for all findings and these are not considered to have had any impact on the integrity of the ALEX data.

Pharmacokinetics

Studies providing pharmacokinetic data

A Population PK report (1080486) based on the BO28984 (ALEX) population was submitted.

Evaluator's conclusions on pharmacokinetics

None of the conclusions based on the population PK modelling have been proposed as new information in the PI and this is appropriate. The analyses did not expand on what was known from the efficacy and safety in the pivotal trial and prognostic factors that are well-established for a range of malignancies.

Pharmacodynamics

No new studies were submitted.

Dosage selection for the pivotal studies

No new studies were submitted.

Efficacy

Studies providing efficacy data

Phase III BO28984 'ALEX' randomised controlled open label trial comparing alectinib with crizotinib in patients with treatment-naïve NSCLC was submitted.

Evaluator's conclusions on efficacy

In this open-label, randomised Phase III trial, alectinib demonstrated clear superiority in the primary efficacy endpoint of investigator-assessed progression-free survival over crizotinib in a population with NSCLC selected for ALK-positivity by the Ventana anti-ALK D5F3 IHC assay. Patients with measurable disease who had not received prior systemic therapy in the advanced/metastatic setting but may have received chemotherapy in the adjuvant or neoadjuvant setting, prior radiation treatment or surgery for localised or for metastatic disease were randomised to receive either alectinib or crizotinib, stratified by race (Asian versus non-Asian), ECOG PS[16] 0/1 versus 2 and presence (yes/no) of CNS metastases. Patients with ECOG performance status 0-2 were eligible, but very few patients with ECOG PS 2 were enrolled, hence efficacy and safety data are limited. Patients with asymptomatic CNS disease were eligible and could have been treated surgically or with radiation treatment or had no prior therapy.

Baseline demographic and disease characteristics were reasonably balanced between the arms and reflect the population likely to present in Australia with ALK-positive lung cancer. Apart from the rates of CNS involvement and the lower proportion of adenocarcinoma subtype in the alectinib arm, the population was not dissimilar to those recruited in other ALK inhibitor first-line Phase III trials. Median PFS was yet to be

[16] ECOG Performance Status (PS): The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used:
0 - Fully active, able to carry on all pre-disease performance without restriction
1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5 – Dead

reached by investigator (primary endpoint) in the alectinib arm and was 11.1 months (95% CI 9.1, 13.1) in the crizotinib arm. The hazard ratio for the risk of progression or death was 0.47 (95% CI 0.34, 0.65; p<0.0001) in favour of alectinib. The results for crizotinib arm were comparable with the 10.9 months reported in the Phase III PROFILE 1014 study comparing crizotinib with chemotherapy for first line systemic therapy of advanced disease.[7] Subgroup analyses confirmed superiority in all but those who were active smokers, and crossed 1 for those of ECOG PS 2. Sensitivity analyses, including an independent review of PFS, were all supportive the primary efficacy endpoint findings. Observed responses were more durable in the alectinib arm than the crizotinib arm.

The benefit of improvement in PFS was most evident in those with CNS progression without prior non-CNS progression and both agents at this time appear active to a similar extent against non-CNS systemic in the absence of CNS progression. The cumulative time to CNS progression was significantly longer in the alectinib arm compared with patients receiving crizotinib but was similar for non-CNS progression. Treatment with alectinib resulted in higher CNS response rates and longer time to CNS progression (based on IRC, Response Evaluation Criteria in Solid Tumors (RECIST) assessments or Revised Assessment in Neuro Oncology (RANO) assessments) of patients with both measurable and non-measurable disease. Although numbers were small, a higher response rate was consistently reported with alectinib, in those who had received prior radiation or had no prior brain radiotherapy, compared with crizotinib.

Objective response rates by investigator assessments were not statistically significant between the two treatments, although numerically more patients achieved a complete response in the alectinib arm. IRC assessments of response rates, including reported complete response (CR), were higher in the alectinib arm than the investigator arm. The median duration of response has yet to be reached in the alectinib arm and was 11.1 months (95% CI: 7.9, 13.0) in the crizotinib arm.

Overall survival data are immature and the effect of treatment switching to alectinib from the crizotinib arm and of subsequent therapies in both arms known to affect survival, may make results difficult to interpret. It is recommended that these results be submitted to the TGA when available.

Selection of patients for treatment

PFS based on a retrospective assessment and limited to those who tested positive for ALK status by Vysis FISH was supportive of a superior treatment effect with alectinib. Notably, results were not available or were negative for 100/303 study participants (61 patients no result possible, 39 patients tested negative), therefore only 66% of patients tested positive for both Ventana IHC/Vysis FISH. The sponsor provided additional data which indicate, that of the 39 tumours that were negative for FISH and positive by IHC treated with either alectinib or crizotinib, a 36% ORR was observed, including a complete response in one patient receiving alectinib and partial responses and stable disease reported by investigators in a further thirteen and ten patients, respectively, with either drug. No Vysis FISH results were presented for 61 samples (20.1% of all samples) due to a combination of limitations with the sample (n=28, 9.2%) or uninterpretable results (n=33, 10.9%). The clinical evaluator did not request a breakdown of the treatment outcomes in this last group but issues with interpretation of the results and availability of an adequate sample, signal limitations with requiring this additional test.

It is noted that the FDA has approved the Ventana ALK D5F3 assay as a companion diagnostic for ceritinib and crizotinib and while not currently seen on the FDA Companion Diagnostics list on their website, the updated US label for alectinib includes this assay in the Clinical Trials section following the very recent first line approval. The data from this trial suggest a high and clinically relevant false negative rate with the Vysis FISH test

(where it was possible to obtain a result), with 12.8% discordance with the ALK IHC results for the overall study population, and 62% of these patients achieving the clinically relevant outcome as a complete or partial remission or stable disease. These patients would not have been deemed eligible based on Vysis FISH for this treatment or for the growing list of effective ALK inhibitors; furthermore, these patients would not be eligible for clinical trials evaluating optimal sequencing or new agents if they have not received prior treatment with ALK inhibitors if eligibility in Australia remains driven by FISH results. The clinical evaluator has recommended inclusion of the efficacy outcomes for those who are ALK IHC-positive/Vysis FISH-negative to inform patients and prescribers. For the following reasons, re-evaluation of the data supporting the need for Vysis FISH confirmation is required: the clinical utility of the VENTANA ALK (D5F3) IHC assay and the significant false positive rate with the Vysis FISH demonstrated in this trial, the use of the IHC to select patients not only in this trial, but also in the first line ceritinib study published this year[15] which resulted in the recent FDA approvals of the Ventana ALK (D5F3) IHC assay as a companion diagnostic for all three ALK inhibitors currently approved in Australia.

The clinical evaluator does not accept the sponsor's rationale for, and self-classification of the Ventana ALK (D5F3) IHC assay as a Class 2 in in-vitro diagnostic medical devices (IVD) and considers it to be a Class 3 IVD given its role in the selection of patients for this cancer therapy in this trial and the use of IHC as pre-screening prior to FISH testing in Australia. It is recommended that an application be required for inclusion as a Class 3 IVD.

Conclusion

Overall, these data support a highly statistically significant and clinically important improvement in efficacy outcomes for patients with metastatic ALK-positive NSCLC when treated with alectinib compared with the current standard of care, crizotinib.

Safety

Studies providing safety data

Safety data are from the pivotal randomised Phase III ALEX study.

Patient exposure

All patients in the ITT Population received at least one dose of study drug and were included in the Safety Population.

The median duration of treatment was notably shorter in patients in the crizotinib arm (10.7 months; range: 0 to 27 months) compared with the alectinib arm (17.9 months; range: 0 to 29 months); this was mainly driven by fewer treatment discontinuations due to disease progression in the alectinib arm (Table 2).

A lower proportion of patients in the crizotinib arm completed > 12 months and > 18 months of study treatment (45% and 27%, respectively) compared with the alectinib arm (66% and 49% patients, respectively).

The mean dose intensity was comparable between treatment arms (92% for crizotinib and 96% for alectinib); however, the proportion of patients in the crizotinib arm (42%) who missed at least one dose of treatment was higher than in the alectinib arm (32%).

Table 2: Study treatment exposure Safety population

	Crizotinib (N=151)	Alectinib (N=152)
Treatment duration (months)		
n	151	152
Mean (SD)	11.8 (7.7)	15.0 (8.7)
Median	10.7	17.9
Min - Max	0 - 27	0 - 29
Treatment duration (months)		
n	151	152
0 - <=6	48 (31.8%)	38 (25.0%)
>6 - <=12	35 (23.2%)	14 (9.2%)
>12 - <=18	27 (17.9%)	26 (17.1%)
>18 - <=24	30 (19.9%)	52 (34.2%)
>24 - <=30	11 (7.3%)	22 (14.5%)
Dose intensity (%)		
n	151	152
Mean (SD)	92.4 (14.1)	95.6 (10.3)
Median	100.0	100.0
Min - Max	42 - 107	45 - 100
Number of doses		
n	151	152
Mean (SD)	694.0 (465.1)	904.1 (525.4)
Median	617.0	1085.5
Min - Max	4 - 1646	26 - 1734
Total cumulative dose (mg)		
n	151	152
Mean (SD)	168301.0 (111989.8)	521320.1 (305243.2)
Median	148000.0	595800.0
Min - Max	1000 - 411500	15600 - 1036800
Missed doses		
n	151	152
No missed doses	87 (57.6%)	103 (67.8%)
At least one missed dose	64 (42.4%)	49 (32.2%)

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day. Dose intensity is the amount of study drug actually received divided by the expected amount.
Data cutoff: 09 February 2017.

Postmarketing data

The study report states, '*As of 29 April 2017, the estimated cumulative market exposure to alectinib is 6275 patients (300 mg BID: Japan, n = 3831; 600 mg BID: US, n = 2238; European Economic Area, n = 47; Rest of World, n = 159) since its International Birth Date of 04 July 2014. The alectinib safety profile in the post-marketing period is consistent with safety data from clinical trials of alectinib*.'

No Periodic Safety Update Report (PSUR) was evaluated as part of this clinical evaluation report.

Evaluator's conclusions on safety

The safety profile of alectinib differs from, but overall, is more favourable than for crizotinib in the treatment of patients who have not received prior systemic therapy for advanced recurrent or metastatic ALK-positive NSCLC. Despite the shorter median duration of treatment with crizotinib of 10.7 months compared with 17.9 months, a greater proportion of patients in the crizotinib arm experienced treatment-related adverse events (AEs) (89% versus 77%), Grade 3 to 5 AEs (50% versus 41%). Adverse events that led to treatment discontinuation (13% versus 11%), dose interruption (25% versus 19%) or dose reduction (21% versus 16%) were higher in the crizotinib arm, but still significant in the alectinib arm.

New safety signals for alectinib include acute kidney injury and weight gain. For the former, the rate of adverse events was much higher than in the crizotinib arm (18% versus 9%) and included two fatal events. At this time, it is not clear if dose reduction or interruption is sufficient to manage the renal toxicity that appeared rapidly in some patients; recurrence with rechallenge was observed across all the clinical trials. Pre-

existing risk factors for diminished renal reserve were present in those who developed acute kidney injury and whether this is associated with a poorer outcome is not clear at this time. The clinical evaluator considers it as important that these questions be addressed, a new Precaution included in the PI for kidney injury including recommendations for management and acknowledgment of any uncertainties surrounding those recommendations. This needs to be examined prospectively as an adverse event of special interest in any future clinical trials, and consideration should be given to a dedicated trial of alectinib in patients with renal impairment or inclusion of a subgroup with baseline renal impairment or risk factors for diminished reserve in future clinical trials to understand this better. In the interim, diminished renal reserve as a risk for renal injury has been included a potential identified risk in the RMP.

Weight gain of greater than 10% was observed in fifteen patients and the mechanism for this is not clear. This is an unusual issue for patients with advanced NSCLC where weight loss is often significant problem and being reported as an adverse event suggests it was problematic to the affected patients. Information regarding the nature of the weight gain (for example, any unusual fat distribution) was not collected and patients do not appear to have been weighed at each visit. It is recommended that data be collected to inform on this in future trials. As this was reported as an adverse event, information should be included in the PI and especially in the Consumer Medicine Information (CMI).

Rates of hepatotoxicity (defined as Hepatocellular or cholestatic damage AEs and abnormal liver laboratory tests, as per the selected adverse events) were similar between the arms and additional risks confirmed for alectinib in this study include drug-induced liver injury (and higher rates of hyperbilirubinaemia than seen with crizotinib).

Additional adverse events confirmed for alectinib and which occurred at a higher rate than in the crizotinib arm include anaemia, photosensitivity, severe myalgia and musculoskeletal pain and creatine phosphokinase (CPK) rise. The following adverse events were also observed with alectinib, but at lower rates than for crizotinib: interstitial lung disease/pneumonitis (although at lower rates than reported in the J-ALEX study) and peripheral oedema.

A decrease from baseline heart rate was almost universal, and 5% of patients were reported as having bradycardia which was clinically significant, in a population where patients with symptomatic bradycardia were excluded, and dizziness was reported in patients on alectinib. The changes in QTcF >30 ms in at least 20% of patients indicate a substantial proarrhythmic potential for alectinib, albeit at a lower level than crizotinib. Based on these findings, it would appear reasonable to require a baseline electrocardiogram (ECG) prior to commencement in order to document any existing risk factors for cardiac risk, and to refer back to in the event of onset of a significant clinical problem. The safety of concomitant medications known to increase the QT interval in patients receiving alectinib is unlikely to have been adequately demonstrated in this clinical trial, as such medications were not permitted in any patients for 14 days prior to enrolment, and then allowed only for those in the alectinib arm.

Gastrointestinal toxicities occurred but at much lower rates than for crizotinib and visual toxicities do not appear to be a significant clinical issue for patients receiving alectinib.

First round benefit-risk assessment

First round assessment of benefit-risk balance

This trial randomised patients to receive either the current standard of care, crizotinib, or alectinib. Compared with crizotinib, alectinib improved progression-free survival, particularly delaying the development or progression of CNS metastases which is a very

significant problem for patients with this disease. CNS response rates were higher and the duration of observed responses was longer and this appears to be one of the key factors in the observed improvement in progression-free survival. Non-CNS disease response rates were not statistically significantly different between the two treatments.

The safety of alectinib compares favourably with crizotinib but there are specific toxicities that are noteworthy including the potential for severe, and sometimes fatal, events of renal failure which appear most common in those with limited renal reserve. Very unusually for patients with NSCLC, weight gain was observed and the reasons for this are not clear. Both of these events require inclusion in the CMI and PI to inform prescribers and patients. Lower rates of some adverse events such as Interstitial lung disease (ILD)/pneumonitis were recorded in the ALEX Phase III study compared with the J-ALEX Phase III study conducted in Japanese patients only, which used a lower dose. The clinical evaluator considers it as important to retain this information rather than replace it as currently proposed by the sponsor.

The false negative rate of the Vysis FISH was significant in this trial with 24/39 patients (8% of the study population) who were IHC-positive/FISH-negative receiving clinical benefit from treatment with either alectinib or crizotinib. With the current algorithm for testing in Australia, a significant proportion of patients (at least 12.8% in this study, but that figure may have been higher given no Vysis FISH test outcomes were available in 61/303 patients) will not be deemed ALK-positive for access to targeted therapies including alectinib, crizotinib and ceritinib. Not only might such patients not be eligible for access to ALK inhibitors, and may be directed to chemotherapy or potentially a programmed death-ligand 1 (PD-1) inhibitor pathway, but may also be ineligible for future clinical trials where prior ALK inhibitor use is required and/or chemotherapy not permitted.

The Ventana ALK (D5F3) IHC assay is currently listed as a Class 2 IVD on the ARTG, which is not consistent with its use in this trial (where it was used for treatment selection) or its recent approvals by the FDA as a companion diagnostic for ALK inhibitors.

First round recommendation regarding authorisation

Subject to satisfactory amendments being made to the PI, it is recommended that the sponsor's proposed indication be approved.

V. Pharmacovigilance findings

Summary

- The most recently evaluated EU-RMP was version 1.1 (date 17 August 2015; Data Lock Point (DLP) 31 July 2015) and ASA version 1.1 (dated October 2016). In support of the extended indications, the sponsor has submitted EU-RMP version 2.1 (date 8 August 2017; DLP 7 July 2017) and Australian Specific Annex (ASA) version 2.0 (August 2017).
- The proposed Summary of Safety Concerns and their associated risk monitoring and mitigation strategies are summarised below in Table 3.

Table 3: Sponsor's proposed Summary of safety concerns

R=Routine and A=Additional

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		R	A	R	A
Important identified risks	Interstitial lung disease/pneumonitis	ü	–	ü	–
	Hepatotoxicity	ü	–	ü	–
	Photosensitivity	ü	–	ü	–
	Bradycardia	ü	–	ü	–
	Severe myalgia and CPK elevations	ü	–	ü	–
Important potential risks*	None				
Missing information#	Treatment in patients with moderate or severe liver impairment	ü	ü	ü	–

Previously evaluated safety summary included:
- Embryo-fetal toxicity as an important potential risk; and
- Long-term safety, treatment in pregnant and lactating women and, patients with moderate or severe renal impairment as missing information.

- Routine pharmacovigilance measures are proposed for all safety concerns. Additional pharmacovigilance activity comprise of an ongoing clinical trial to assess the effect of hepatic impairment on the pharmacokinetics of alectinib. The pharmacovigilance plan is acceptable.
- Only routine risk minimisation activities are proposed and, it is considered acceptable.

Recommendations

There were no recommendations from the RMP Evaluator and no outstanding issues.

The RMP was considered to be satisfactory.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system. Proposed wording:

> The alectinib EU-Risk Management Plan (RMP) (version 2.1; date 8 August 2017; DLP 7 July 2017), with Australian Specific Annex (version 2.0; date August 2017), included with submission PM-2017-03224-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of Periodic Safety Update Reports (PSURs). Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared within ninety calendar days of the data lock point for that report.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

Efficacy

Pivotal trial design

Study BO28984, or the 'ALEX' trial, is an ongoing Phase III, randomised, open-label trial which randomised 303 patients screened from 97 sites in 29 countries globally, including 16 patients from 5 Australian sites.

The reason for the open-label design was to improve tolerability and adherence, given the large number of tablets that would be required for double blinding, as well as the complexity of dose reduction, given the different dosing and tablet sizes used in each arm. Although not ideal, open- label design is not likely to have confounded outcomes measured by blinded independent central review (BICR).

Outcomes based on tumour measurement were assessed using the RECIST v1.1 criteria.

Recruitment occurred between August 2014 and January 2016.

The main cut-off date was 9 February 2017.

The median follow-up was 17.6 months (range: 0.3 to 27.0 months) in the crizotinib arm and 18.6 months (range: 0.5 to 29.0 months) in the alectinib arm. The Trial design is summarised in Table 4 below.

Table 4: Summary of pivotal trial design

	Details
Patient population	n=303 (alectinib arm: 152; crizotinib arm: 151) Inclusion criteria (abridged) Consenting adults with Stage IIIB or IV NSCLC confirmed by histology or cytology, that had not previously been treated systemically ALK positivity per the Ventana immunohistochemistry assay which has been approved by the FDA as a companion diagnostic for crizotinib Measurable disease on RECIST v1.1 criteria ECOG performance score 0 – 2, adequate haematological and renal function, non-reproductive Life expectancy 12+ weeks
	Exclusion criteria (abridged) Untreated/unstable brain metastases or leptomeningeal disease Malabsorptive GI disorder, liver disease, previous significant malignancy within 3 years, other significant medical conditions QT prolongation, symptomatic bradycardia or coadministration of prolonging medications Coadministration of potent CYP3A inhibitors or inducers Organ transplant, HIV positivity Ongoing toxicity from prior therapies (CTCAE grade 3 or higher)
Intervention	600 mg BD alectinib
Comparator	250 mg BD crizotinib
Endpoints	Primary Progression-free survival (PFS) [investigator assessed] Key secondary PFS [independent review committee (IRC) assessed] Time to CNS progression according to RECIST criteria [IRC assessed] Objective response rate (ORR) and duration of response (DOR) [investigator assessed] Overall survival (OS) CNS ORR (CORR) and CNS DOR (CDOR) [IRC assessed] – defined as proportion of patients achieving CR or PR of baseline CNS lesions, and time from CNS response to CNS progression of disease, respectively. Other secondary Safety and tolerability Pharmacokinetics (PK)

Sample size

286 subjects were to be randomised in in a 1:1 ratio. This sample size would result in at least 80% power to detect a HR of 0.65 for alectinib versus crizotinib (that is, an increase from 10.9 months median PFS to 16.8 months) at a two-sided α=0.05.

ALK positivity was tested at a central laboratory using Ventana anti-ALK (D5F3) immunohistochemistry (IHC) testing, which during the progress of the trial was approved by the FDA as a companion diagnostic for crizotinib. Positivity on IHC testing was required for study entry but sufficient tumour sample was required for both IHC and FISH Vysis® ALK Break Apart FISH Probe Kit (Abbott) and FISH testing was performed subsequently to study entry. Use of the IHC assay as a screening tool, with subsequent validation using FISH testing is currently required for funded access to anti-ALK therapies in Australia.

Tumour imaging by computed tomography (CT) or Magnetic Resonance Imaging (MRI), including of the brain, was done at baseline and again every 8 weeks until progression. The IRC performed two separate assessments for each time point; one for systemic disease overall and one for CNS endpoints specifically.

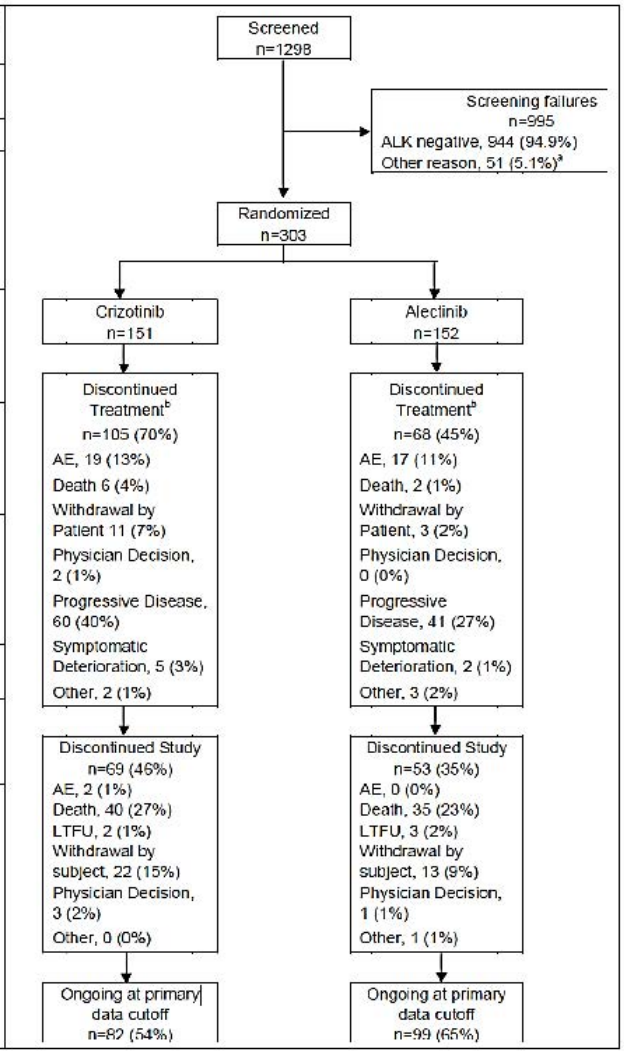
Cross-over In-study crossover was not permitted. Subsequent lines of therapy are not yet reported, as overall survival (OS) data are immature. Submission of these results, when available, will be a condition of registration.

Baseline characteristics and patient disposition

The following table summarises the baseline characteristics of the pivotal study population and patient disposition in ALEX study.

Table 5: Baseline characteristics of the pivotal study population (left) and patient disposition summary, from the study report for the ALEX trial (right)

	Crizotinib N=151	Alectinib N=152
Median age (range)	54 (18, 91)	58 (25, 88)
Male	42.4%	44.7%
ECOG		
0	35.1%	28.3%
1	56.3%	62.5%
0 or 1	93.4%	93.4%
2	6.6%	6.6%
Histology		
Adenoca	98%	87%
NOS	3%	11%
Large cell	0%	2%
Stage		
IIIA	0%	2%
IIIB	2%	3%
IV	98%	95%
Smoking status		
Current/former	75%	86%
never	25%	14%
Stable brain mets	15%	10%
Previous (neo) adj systemic therapy	7%	8%
PD-L1 TPS		
<1%	35%	37%
1%-49%	32%	37%
50+%	33%	27%



Exposure

Table 6 summarises the duration of treatment (exposure) in the two arms.

Table 6: Duration of treatment exposure

	Crizotinib N=151	Alectinib N=152
Duration of treatment exposure		
Mean, months (standard deviation)	11.8 (7.7)	15.0 (8.7)
Median, months (min, max)	10.7 (0, 27)	17.9 (0, 29)

Results

Primary efficacy endpoint

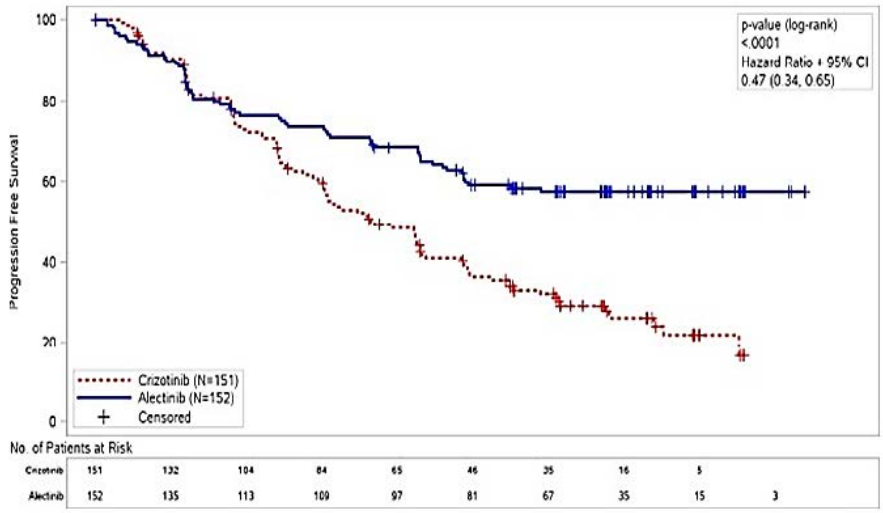
Table 7 and Figure 1 below summarise the results for the primary efficacy endpoint.

Table 7: Primary efficacy endpoint in the intention-to-treat (ITT) population

	Crizotinib N=151	Alectinib N=152
PFS [investigator assessed]		
Patients with PFS event (%)	102 (67.5)	62 (40.8)
Median PFS, months [95% CI]	11.1 [9.1-13.1]	NE [17.7, NE]
HR [95%CI] (p value*)	0.47 [0.34, 0.65] (<0.0001*)	

CI = confidence interval; HR = hazard ratio; NE = not estimable
* By stratified log-rank test
Strata = race (Asian vs non-Asian) and CNS metastases at baseline by IRC

Figure 1: Kaplan-Meier curve for the primary efficacy endpoint in the ITT population



Secondary efficacy endpoints

Table 8 below summarises the results for the secondary efficacy endpoints.

Table 8: Secondary efficacy endpoints in the ITT population

	Crizotinib N=151	Alectinib N=152
PFS [IRC assessed]		
Patients with PFS event (%)	92 (60.9)	63 (41.4)
Median PFS/time to event, months [95% CI]	10.4 [7.7, 14.6]	25.7 [19.9, NE]
HR [95%CI] (p value)*	0.50 [0.36, 0.70] (p<0.0001)*	
Time to CNS progression [IRC assessed, by RECIST v1.1]		
Patients with CNS progression, without	68 (45.0)	18 (11.8)

	Crizotinib N=151	Alectinib N=152
prior non-CNS progression (%)		
HR [95%CI] (p value)	0.16 (0.10, 0.28) (p<0.0001)**	
ORR [investigator assessed]		
Responders (ORR , %) per investigator	114 (75.5)	126 (82.9)
Difference [95% CI] (p value)***	7.40 [-1.71, 16.50] (0.0936)***	
Complete responses (%)	*2 (1.3)*	*6 (3.9)*
DOR [investigator assessed]		
Responders with event/responders (%)	73/114 (64)	40/126 (31.7)
Median DOR, months [95% CI]	11.1 [7.9,13.0]	NE [NE]
HR [95%CI] (p value)*	0.36 [0.24, 0.53] (<0.0001)*	
OS**		
Patients with event (OS, %)	40 (26.5)	35 (23.0)
HR [95%CI] (p value)*	0.76 (0.48, 1.2) (p=0.2405)*	
CORR [IRC assessed, by RECIST v1.1]		
Responders (% [95% CI])	15 (26 [15, 39])	38 (59 [46, 71])
Difference in CORR [95% CI] (p value)***	33.5 [17.0, 50.0] (0.0002)***	
Complete responses (%)	*5 (8.6)*	*29 (45.3)*
CDOR [IRC assessed, by RECIST v1.1]		
Responders with event/responders (%)	13/15 (86.7)	11/38 (28.9)
Median CDOR, months [95% CI]	3.7 [3.2, 6.8]	NE [17.3, NE]
HR [95%CI] (p value)*	0.23 [0.10, 0.53] (0.0002)*	

CI = confidence interval; HR = hazard ratio; NE = not estimable
* By stratified log-rank test
** stratified cause-specific hazard ratio and stratified cause-specific log rank test from competing risk analysis
*** stratified Mantel-Haenszel test
**** As the previous key secondary endpoint of investigator-assessed ORR in the pre-specified hierarchy was not statistically significant, OS was not formally tested
Strata = race (Asian vs non-Asian) and CNS metastases at baseline by IRC

Safety

An overview of the frequency, severity and outcomes of adverse events (AEs) in the pivotal trial is given in Table 9. The trial was open label, which could have led to various biases including reporting and attribution.

Despite the shorter duration of treatment, there was a higher rate of treatment-related AEs (89% versus 77%), Grade 3 to 5 AEs (50% versus 41%), AEs that led to treatment discontinuation (13% versus 11%), AEs that led to dose interruption (25% versus 19%) and AEs that led to dose reduction (21% versus 16%) in the crizotinib arm.

Table 9: Overview of adverse events in the ALEX trial

	Crizotinib N=151	Alectinib N=152
Total number of patients with ≥ 1 AE, n (%)	146 (97%)	147 (97%)
Total number of events, n	1365	1196
Total number of patients with ≥ 1, n (%)		
AE with fatal outcome (Grade 5)	7 (5%)	5 (3%)
Grade ≥3 AE	76 (50%)	63 (41%)
Serious AE	44 (29%)	43 (28%)
AE leading to treatment discontinuation	19 (13%)	17 (11%)
AE leading to dose reduction	31 (21%)	24 (16%)
AE leading to drug interruption	38 (25%)	29 (19%)

The rate of serious AEs was similar between arms. Grade 3+ adverse events and events with fatal outcome occurred more frequently in the crizotinib arm and death was considered to be related to study treatment by the investigator in 2 patients in the crizotinib arm versus zero in the alectinib arm. The most common Grade 3+ adverse events in the alectinib group were increased alanine aminotransferase (ALT) (5%), increased aspartate aminotransferase (AST) (5%) and anaemia (5%). For the crizotinib group, the most common Grade 3+ adverse events were increased ALT (15%) and increased AST (11%).

Selected AEs were given particular attention in the study, based on existing previous safety data for alectinib and crizotinib. The overall rates of selected AEs are summarised in Table 10.

Table 10: Overview of selected adverse events in the ALEX trial

	Crizotinib (N=151)				Alectinib (N=152)			
Selected Adverse Events	All Grades	Grade 3/4/5	Serious	Leading to Treatment Discontinuation	All Grades	Grade 3/4/5	Serious	Leading to Treatment Discontinuation
Total number of patients with at least one adverse event	142 (94.0%)	53 (35.1%)	15 (9.9%)	15 (9.9%)	127 (83.6%)	35 (23.0%)	15 (9.9%)	13 (8.6%)
Gastrointestinal Tract Adverse Events	120 (79.5%)	10 (6.6%)	5 (3.3%)	0	84 (55.3%)	2 (1.3%)	0	0
Muscular Adverse Events, CPK Elevations	46 (30.5%)	3 (2.0%)	0	0	58 (38.2%)	5 (3.3%)	1 (0.7%)	0
Hepatocellular or Cholestatic Damage AEs and Abnormal Liver Function Tests	50 (33.1%)	26 (17.2%)	4 (2.6%)	9 (6.0%)	48 (31.6%)	17 (11.2%)	3 (2.0%)	7 (4.6%)
Skin Disorders	38 (25.2%)	0	0	0	41 (27.0%)	2 (1.3%)	1 (0.7%)	0
Vision Disorders	50 (33.1%)	0	1 (0.7%)	0	12 (7.9%)	0	0	0
Hematologic Abnormalities	25 (16.6%)	9 (6.0%)	0	0	36 (23.7%)	8 (5.3%)	2 (1.3%)	1 (0.7%)
Abnormal Kidney Function Adverse Events	13 (8.6%)	2 (1.3%)	1 (0.7%)	0	28 (18.4%)	7 (4.6%)	7 (4.6%)	4 (2.6%)
Interstitial Lung Disease	9 (6.0%)	3 (2.0%)	5 (3.3%)	5 (3.3%)	3 (2.0%)	0	2 (1.3%)	1 (0.7%)
QT Interval Prolongation	7 (4.6%)	5 (3.3%)	0	1 (0.7%)	0	0	0	0

For frequency counts by selected adverse event, multiple occurrences of the same AE in an individual are counted only once.

AEs seen in the ALEX trial were principally in keeping with the known safety profile of alectinib.

AEs that were reported at similar rates between arms were constipation, fatigue, arthralgia and rash.

AEs that occurred with *crizotinib* at an incidence at least 5% higher than in the alectinib arm included nausea (48% versus 14%), diarrhoea (45% versus 12%), vomiting (38% versus 7%), ALT elevation (30% versus 15%), AST elevation (25% versus 14%), GGT elevation (7% vs.1%), peripheral oedema (28% versus 17%), dizziness (14% versus 8%), dysgeusia (19% versus 3%), visual impairment (12% versus 1%), blurred vision (7% versus 2%), photopsia (6% versus 0%) and alopecia (7% versus 1%).

AEs that occurred with *alectinib* at an incidence at least 5% higher than in the crizotinib arm included bilirubinaemia (15% versus 1%), weight gain (10% versus 0%), myalgia (16% versus 2%), 'musculoskeletal pain' (7% versus 2%), anaemia (20% versus 5%) and photosensitivity reaction (5% versus 0%).

Hyperbilirubinaemia, myalgia, musculoskeletal pain anaemia, and photosensitivity reaction are known to occur with alectinib and are described in the alectinib PI. Two new safety signals (acute kidney injury and weight gain) emerged from the study and have been incorporated into the PI appropriately. Acute kidney injury was reported in four patients (2.6%) in the alectinib arm but examination of the case narratives does not indicate a clear enough association with alectinib to warrant inclusion under Precautions based on current information.

The clinical evaluator's conclusion was that:

> *The safety profile of alectinib differs from, but overall, is more favourable than for crizotinib in the treatment of patients who have not received prior systemic therapy for advanced recurrent or metastatic ALK-positive NSCLC.*

Risk management plan

TGA conducted an evaluation of the RMP. The RMP was considered to be satisfactory. The evaluator had no recommendations and there were no outstanding issues.

Risk-benefit analysis

Delegate's considerations

The following table summarises the Delegate's considerations of benefits and associated uncertainties, and harms and associated uncertainties, and a benefit risk balance.

Table 11: Delegate's considerations

Benefits and associated uncertainties	According to the ALEX study, compared with crizotinib, alectinib improved investigator-assessed progression-free survival (PFS), the pre-specified primary endpoint, by 53% (hazard ratio [HR] 0.47; 95% CI 0.34-0.65; P <.0001). Median PFS was not reached in the alectinib arm and was just over 11 months in the crizotinib arm. The HR for PFS by blinded independent central review (secondary endpoint) was 0.50 (0.36, 0.70), p<0.0001. The median PFS was 26 months in the alectinib arm and 10 months in the crizotinib arm. De novo metastases occurred in 12% of patients in the alectinib arm and 45% in the crizotinib arm: HR=0.16 (0.10, 0.28), p<0.0001. At the time of data cutoff, about one-quarter of the patients had died: alectinib: 23%; crizotinib: 27%; HR=0.76 (0.48, 1.20), not statistically significant. More mature data on overall survival and post- progression treatments is expected.

Harms and associated uncertainties	Adverse events (AEs) seen in the ALEX trial were principally in keeping with the known safety profile of alectinib. AEs that were reported at similar rates between arms were constipation, fatigue, arthralgia, and rash. Gastrointestinal (GI) toxicity was better with alectinib than crizotinib. AEs that occurred more frequently with crizotinib (at least 5% higher incidence) included nausea (48% versus 14%), diarrhoea (45% versus 12%), vomiting (38% versus 7%), ALT elevation (30% versus 15%), AST elevation (25% versus 14%), gamma-glutamyltransferase (GGT) elevation (7% versus 1%), peripheral oedema (28% versus 17%), dizziness (14% versus 8%), dysgeusia (19% versus 3%), visual impairment (12% versus 1%), blurred vision (7% versus 2%), photopsia (6% versus 0%) and alopecia (7% versus 1%) AEs that occurred more frequently with alectinib (at least 5% higher incidence) included bilirubinaemia (15% versus 1%), weight gain (10% versus 0%), myalgia (16% versus 2%), 'musculoskeletal pain' (7% versus 2%), anaemia (20% versus 5%) and photosensitivity reaction (5% versus 0%). The rate of serious AEs was similar between arms: 29% with alectinib and 28% with crizotinib. Grade 3+ adverse events occurred in 41% (alectinib) and 50% (crizotinib) of patients. The most common Grade 3+ adverse events in the alectinib group were increased ALT (5%), increased AST (5%), and anaemia (5%). For the crizotinib group, the most common Grade 3+ adverse events were increased ALT (15%) and increased AST (11%). Adverse events leading to treatment interruption (19% vs 25%), dose reduction (16% versus 21%) and treatment discontinuation (11% versus 13%) were more common with crizotinib. Adverse events leading to death occurred in 5 (3%) versus 7 (5%) of patients. Death was considered to be related to study treatment in 0 vs 2 patients.
Benefit-risk balance	Compared to crizotinib, alectinib has superior efficacy, especially in the central nervous system, and at least similar but likely lower toxicity (especially lower GI toxicity).

Benefit-risk balance

- Statistically significant benefits in PFS, duration of response (DOR), time to CNS progression, CNS objective response rate (C-ORR) and CNS duration of response (C-DOR) have been demonstrated by the ALEX study. These benefits are of large magnitude and particular clinical significance given that the most common site of relapse/progression in crizotinib-treated patients is in the CNS.
- The safety profile of alectinib also appears to be overall favourable compared to crizotinib, although the safety profiles of the two differ.

The benefits of alectinib treatment, therefore, clearly outweigh the risks, for the proposed usage.

Conditions of registration

The standard conditions of registration should apply, including those proposed in the RMP evaluation.

Product information

The proposed PI is satisfactory.

Response from sponsor

The following is the sponsor's response to two matters raised on 19 January 2018 by the Delegate:

1. *Why has the EMA retained the second-line sub-part of the indication, when this could be assumed to be a subset of 'use in ALK+ NSCLC'. (The FDA did not retain the second-line sub-part of the indication).*

The approved indication for Alecensa in EU (including two separate statements for first and second-line treatment) was proposed by the sponsor and is not based on a request by EMA during the evaluation. The sponsor applied for different indication statements in EU and USA, for consistency with the indications previously approved for other ALK inhibitors in the respective regions.

2. *When is mature data on OS and post-progression treatments from the ALEX trial expected to be available?*

The final OS analysis for the ALEX study is event driven. It is planned to perform a survival follow-up analysis once approximately 50% of patients (that is, 143 patients) have died. Based on the current event rate (with associated uncertainty) the final OS analysis is expected to be available by second quarter 2020. This analysis will also include information on post-progression treatment.

The sponsor agrees with the summary and the conclusions in the Delegate's Overview (see above) and has no other comments.

Advisory committee considerations

The Delegate did not seek advice from the Advisory Committee on Medicines on this application.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Alecensa containing 150 mg alectinib in hard capsules, indicated for:

> *Alecensa is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, locally advanced or metastatic non-small cell lung cancer (NSCLC).*

Specific conditions of registration applying to these goods

The alectinib EU-Risk Management Plan (RMP) (version 2.1; date 8 August 2017; DLP 7 July 2017), with Australian Specific Annex (version 2.0; date August 2017), included with submission PM-2017-03224-1-4, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI for Alecensa approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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