

5.02 BRIGATINIB,

Tablet 30 mg, 90 mg, 180 mg,

**Pack containing 7 tablets brigatinib 90 mg and 21
tablets brigatinib 180 mg,**

Alunbrig[®],

Takeda Pharmaceuticals Australia Pty Ltd.

1 Purpose of Application

- 1.1 The submission requested a Section 85 (General Schedule), Authority Required (telephone) listing for brigatinib, as monotherapy in patients with locally advanced (Stage IIIB) or metastatic (Stage IV) anaplastic lymphoma kinase (ALK)-positive non-squamous (NS) or not otherwise specified (NOS) non-small cell lung cancer (NSCLC) and a World Health Organization (WHO) performance status of 2 or less. The requested listing was agnostic to the line of therapy. Brigatinib currently has TGA registration for use following treatment with crizotinib in the second-line setting; the proposed PBS listing was thus broader than the approved TGA indication.
- 1.2 The submission presented a cost-minimisation analysis (CMA), on the basis that brigatinib, titrated to 180 mg orally per day (90 mg per day for first seven days) was non-inferior to alectinib in terms of efficacy and safety. An indirect comparison of brigatinib with alectinib, using crizotinib as the common reference, was presented for treatment of naïve patients in the first-line setting. A naïve indirect comparison between brigatinib and alectinib was presented for treatment of patients with prior exposure to a tyrosine kinase inhibitor (TKI) in the second-line setting.
- 1.3 The key components of the clinical issues addressed by the submission are shown in Table 1.

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Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with ALK-positive locally advanced (Stage IIIB) or metastatic (Stage IV) non-squamous (NS) or not otherwise specified (NOS) NSCLC and a WHO performance status of 2 or less.
Intervention	Brigatinib (Alunbrig®), titrated to 180 mg (1 x 180 mg tablet) once daily until progression.
Comparator	Alectinib 600 mg (4 x 150 mg capsules) twice daily until progression (total daily dose 1,200 mg).
Outcomes	Progression free survival (PFS); objective response rate (ORR); duration of response (DOR); CNS response outcomes (CNS ORR and DOR); overall survival (OS); quality of life (QoL); safety and tolerability.
Clinical claim	In patients with ALK-positive, locally advanced or metastatic NSCLC, brigatinib provides at least similar efficacy to alectinib for key clinical outcomes (ORR, DOR, PFS and OS). Brigatinib is associated with a different but overall non-inferior safety and tolerability profile to that seen with alectinib and other ALK targeted TKIs. Emerging clinical data demonstrate that these therapeutic relativities are likely to hold in both ALK inhibitor naïve and prior TKI (crizotinib) experienced patients.

Abbreviations: ALK = anaplastic lymphoma kinase; CNS = central nervous system; DOR = duration of response; mg = milligram; NSCLC = non-small cell lung cancer; NS = non-squamous; NOS = not otherwise specified; PFS = progression free survival; ORR = objective tumour response rate; OS = overall survival; QoL = quality of life; TKI = tyrosine kinase inhibitor; WHO = World Health Organization

Source: Table 1.1, p.3 of the submission.

2 Requested listing

- 2.1 Suggestions and additions proposed by the Secretariat to the requested listing criteria are added in italics and suggested deletions are crossed out with strikethrough.
- 2.2 The submission proposed that a special pricing arrangement (SPA) apply, consistent with the arrangements applied to alectinib, ceritinib and crizotinib. The proposed published Dispensed Price for Maximum Quantity (DPMQ) for brigatinib was \$ [REDACTED] for all four presentations. The submission proposed a flat pricing structure with the same cost per day across the different pack sizes, except for patients on the lowest dose reduction step (i.e. 60 mg daily, using the 30 mg strength). The submission did not propose an effective price for brigatinib, noting that this would be determined by the cost-minimised price to the effective price for alectinib.
- 2.3 The current price for alectinib was determined on a cost-minimisation basis with ceritinib at a dose of 750 mg daily. Since that time, the TGA-approved daily dose of ceritinib has been amended to 450 mg daily.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BRIGATINIB Initiation pack containing 7 x 90 mg tablets and 21 x 180 mg tablets 90 mg tablet [7] (&) 180 mg tablet [21], 1 pack	1	0	\$ [REDACTED] (Published)	Alunbrig® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition:	non-small cell lung cancer (NSCLC)

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PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must be as monotherapy, AND</p> <p>The condition must be non-squamous type NSCLC <i>non-small cell lung cancer</i> (NSCLC) or not otherwise specified (NOS) type NSCLC, AND</p> <p>Patient must have a WHO performance status of 2 or less.</p>
Population criteria:	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.
Administrative Advice:	<p>No increase in the maximum quantity or number of units may be authorised.</p> <p>No increase in the maximum number of repeats may be authorised.</p> <p>Special Pricing Arrangements apply.</p>

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BRIGATINIB			\$ [REDACTED]	Alunbrig® Takeda Pharmaceuticals Australia Pty Ltd
30 mg tablets, 28	4	1	(Published)	
90 mg tablets, 28	1	1		
180 mg tablets, 28	1	1		

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition:	non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Clinical criteria:	<p>The treatment must be as monotherapy, AND</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition, AND</p> <p>Patient must not develop disease progression while receiving PBS-subsidised treatment with this drug for this condition.</p>
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised.

	No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.
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- 2.4 The submission proposed a PBS listing for brigatinib that was line agnostic. However, this is broader than the currently approved TGA indication, which is limited to patients previously treated with crizotinib. The Pre-Sub-Committee Response (PSCR) and the pre-PBAC response argued that the PBAC previously recommended the listings of ceritinib and alectinib without any restrictions to line of therapy that were discordant to the TGA approved indications at the time of PBAC consideration, largely based on evidence in a later-line setting (paragraph 7.3, alectinib Public Summary Document (PSD), July 2017).
- 2.5 The proposed listing requires evidence of ALK gene rearrangement by fluorescence in situ hybridisation (FISH) testing, in order to access PBS subsidised treatment with an ALK inhibitor. Currently, FISH testing for ALK status is funded by the Medicare Benefits Scheme (MBS) under Item 73341. MBS Item 73341 specifies use for access to crizotinib, ceritinib or alectinib under the PBS; brigatinib is not a listed drug to be accessed via MBS Item 73341. Should brigatinib be listed as requested – line-agnostic – then patients would be able to access it first-line and therefore would require a determination of their ALK status in order to qualify for brigatinib on the PBS. Thus, the sponsor lodged the minor streamlined co-dependent application to add brigatinib to MBS Item 73341 and is expected to be considered by the Medical Services Advisory Committee (MSAC) at its meeting on 28-29 November 2019.

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Background

Registration status

- 3.1 Brigatinib was approved for registration by the TGA on 6 March 2019 for the treatment of adult patients with ALK positive advanced NSCLC previously treated with crizotinib.
- 3.2 The submission noted that the sponsor would submit the data for the first-line indication to the TGA in February 2020, with registration expected in March 2021. The completion of ALTA-1L study was due in September 2019.

Previous PBAC consideration

Committee-In-Confidence information

- 3.3 A summary of the previous considerations of these ALK-TKIs by the PBAC is provided in Table 2, along with the current considerations of brigatinib and lorlatinib.

Table 2: Summary of evidence submitted for ALK positive NSCLC

	Crizotinib (Nov 2014)	Ceritinib (Nov 2016)	Alectinib (Jul 2017)	Brigatinib (Nov 2019)	Lorlatinib (Nov 2019)
Requested PBS restriction	2 nd line (after platinum)	2 nd line (after TKI i.e. crizotinib)	2 nd line (after TKI i.e. crizotinib, ceritinib)	1 st and 2 nd line	ALK positive NSCLC previously treated with one or more ALK TKIs.
TGA approval at time of submission	No restriction on line of therapy.	2 nd line	2 nd line	2 nd line	██████████ ██████████
Evidence presented to PBAC	2 nd line (after platinum) (RCT)	2 nd line (RCT)	2 nd line (single arm)	1 st line (ITC of RCTs) and 2 nd line (single arm)	██████████ ██████████
PBAC decision	No restriction on line of therapy	No restriction on line of therapy	No restriction on line of therapy	NA	NA

Abbreviations: ALK = anaplastic lymphoma kinase; ITC = indirect treatment comparison; NR = not reported; ITC = indirect treatment comparison; NSCLC = non-small cell lung cancer; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; RTC = randomised controlled trial; TKI = tyrosine kinase inhibitor.

Source: compiled during the evaluation

End Committee-In-Confidence information

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 NSCLC accounts for around 80%-90% of all lung cancers (Planchard et al., 2019); with 3-5% of these cases being associated with ALK gene rearrangements (Gainor et al., 2013). About 70% of NSCLC patients have advanced (Stage IIIB/IV) disease at diagnosis (Besse et al., 2014). Patients with ALK-positive NSCLC typically present with more metastatic sites than those with other disease subtypes. Central nervous system (CNS) involvement in ALK-positive NSCLC is common, with 20%-40% of patients having brain metastases at diagnosis (NCI, 2019).

4.2 Brigatinib is a TKI, which inhibits multiple kinases including ALK, ROS1 and insulin-like growth factor 1 receptor. The submission noted that, among these kinases, brigatinib is most active against ALK. Three TKIs (crizotinib, ceritinib, and alectinib) are currently available on the PBS for the treatment of patients with the proposed indication. The submission requested that brigatinib be listed for the treatment of treatment naïve patients with locally advanced or metastatic ALK-positive NSCLC, and those patients who have disease progression following treatment with a prior TKI. The population requested by the submission was well described and the same as previous submissions to the PBAC.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The submission nominated alectinib as the main comparator for brigatinib in both the first-line and second-line treatment settings. The submission's key arguments provided in support of this nomination were:
- Alectinib has become established as the standard of care among both TKI naïve and crizotinib refractory patients. The submission supported this argument by providing data analysed from PBS services that alectinib accounts for 78% of the market. The ESC noted that alectinib is the preferred first-line ALK-TKI treatment (NCCN guidelines v4, 2019).
 - The increasing use of alectinib is consistent with its more tolerable adverse events profile. The ESC recalled that alectinib was recommended for PBS listing on the basis of non-inferiority to ceritinib, not superiority.
- 5.2 The ESC noted that alectinib is the preferred TKI in the first-line setting in clinical guidelines and the ESC noted that the PBS statistics suggested that alectinib was the most widely used therapy in the first-line setting. The ESC considered that alectinib and ceritinib would be the therapies most replaced by brigatinib (since crizotinib requires written authorisation, and chemotherapy is likely to be used only from third-line onwards, albeit in a small number of patients).
- 5.3 The submission proposed ceritinib as a potential supplementary comparator. The ESC agreed ceritinib was an alternative comparator, but noted the submission did not provide evidence comparing brigatinib with ceritinib. The PSCR noted that there was a lack of comparable data of ceritinib in the post-alectinib treatment setting. Although alectinib was previously recommended on a cost-minimisation basis compared with ceritinib 750 mg, the ESC noted that the TGA recommended dose for ceritinib is now 450 mg and ceritinib 450 mg is less costly than alectinib.
- 5.4 The Secretariat examined the utilisation and the average daily dose for ceritinib based on the PBS administrative claims data. The market share summary for the most recent 12 months at the time of analysis (1 October 2018 to 30 September 2019) showed the scripts of ceritinib comprising 3.3% (n=104) of the total scripts (n=3163) for ALK inhibitors in NSCLC. Since ceritinib first listed, the analysis found that the median daily dose for ceritinib was 750 mg (mean daily dose of 786.20 mg).
- 5.5 Under Section 101(3B) of the *National Health Act (1953)* where therapy involving the use of a particular drug or medicinal preparation, or a class of drugs and medicinal preparations, is substantially more costly than an alternative therapy or alternative therapies, whether or not involving the use of other drugs or preparations, the Committee shall not recommend to the Minister that the drug, preparation or class be made available as pharmaceutical benefits under this Part unless the Committee is satisfied that the first-mentioned therapy, for some patients, provides a significant

improvement in efficacy or reduction of toxicity over the alternative therapy or therapies. The PBAC considered that alectinib and ceritinib were alternative therapies.

- 5.6 The submission did not consider the potential for lorlatinib, which was considered at the November 2019 meeting for use in ALK-positive NSCLC following treatment with one or more ALK TKIs, as a near-market comparator.
- 5.7 The main differences between brigatinib and the comparators are summarised as:
- Pharmacological mechanism of action: brigatinib also targets EGFR, whereas alectinib targets RET; there are no additional targets for ceritinib; and lorlatinib also targets ROS1.
 - TGA indication: alectinib and ceritinib are currently indicated for use in locally advanced and metastatic NSCLC as first-line therapy while the approved TGA indications were for use in the second-line setting at the time of PBAC consideration. Brigatinib is only indicated for use post-crizotinib.
 - Treatment line based on PBS restrictions: brigatinib is requesting a PBS listing that is line-agnostic, consistent with that for alectinib and ceritinib, while that requested for lorlatinib is line dependent.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (70), health care professionals (1) and organisations (4) via the Consumer Comments facility on the PBS website. The comments described the need for an additional treatment option with new ALK inhibitor to be on the PBS for patients who were concerned about treatment options when they become refractory to the current therapies, highlighting the benefits of treatment with ALK inhibitors that include a longer overall survival, delayed chemotherapy treatment, manageable side effect profiles compared to other treatment options, and improved quality of life. The PBAC noted that brigatinib was not available through a patient access program but considered that consumer comments were supportive of listing for brigatinib.

- 6.3 The PBAC noted the advice received from Lung Foundation Australia and Rare Cancers Australia that the use of brigatinib may provide the added survival and improved quality of life with its high response rate in patients with brain metastases that is very important in this disease as failure to control disease in the brain is often the cause of deterioration in quality of life and eventual mortality in these patients.
- 6.4 The Medical Oncology Group of Australia (MOGA) also expressed its support for the brigatinib submission on the basis of improved PFS and QoL¹ benefits presented in ALTA-1L² trial.

Clinical trials

- 6.5 In the first-line setting, the submission was based on an indirect treatment comparison (ITC) of brigatinib and alectinib, using crizotinib as a common comparator. This was informed by one phase 3 randomised controlled trial (RCT) of brigatinib versus crizotinib (ALTA-L1; NCT02737501, N=275) and one phase 3 RCT of alectinib versus crizotinib (ALEX; NCT02075840, N=303).
- 6.6 In the second-line setting, the submission was based on a naïve comparison of one single arm phase 2 study (Study 201-ALTA; NCT02094573, N=222) comparing two different doses of brigatinib (90 mg arm or Arm A, versus 180 mg arm or Arm B) and one Phase 3 RCT trial of alectinib versus chemotherapy (ALUR; NCT02604342, N=107). The non-inferiority claim of efficacy and safety of brigatinib was based on the 180 mg arm of Study 201-ALTA compared with the alectinib arm in ALUR. The naïve comparison used in the second-line setting did not include a common reference; Study 201-ALTA was a comparison of brigatinib doses, while ALUR compared alectinib with chemotherapy – thus there was no common reference across those studies.
- 6.7 Details of the trials presented in the submission are provided in the table below.

Table 3: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Brigatinib studies		
ALTA-1L	A Phase 3 Multicenter Open-label Study of Brigatinib (AP26113) versus Crizotinib in Patients with ALK-positive Advanced Lung Cancer. Clinical Study Report	13 September 2018
	Popat, S., Tiseo, M., Gettinger, S. et al. 2016. "ALTA-1L (ALK in lung cancer trial of Brigatinib in 1st Line): A randomised, phase 3 trial of brigatinib (BRG) versus crizotinib (CRZ) in tyrosine kinase inhibitor (TKI)-naïve, advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC)"	Annals of Oncology 27 (Supplement 6).

¹ Campelo RG, Lin HM, Perol M, et al: Health-related quality of life (HRQoL) results from ALTA-1L: Phase 3 study of brigatinib vs crizotinib as first-line (1L) ALK therapy in advanced ALK+ non-small cell lung cancer (NSCLC). Journal of Clinical Oncology 37:9084-9084, 2019

² Camidge DR, Kim HR, Ahn M-J, et al: Brigatinib versus Crizotinib in ALK-Positive Non-Small-Cell Lung Cancer. New England Journal of Medicine 379:2027-2039, 2018

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Trial ID	Protocol title/ Publication title	Publication citation
	Tiseo, M., Popat, S., Gettinger, S. N. et al. 2017. "Design of ALTA-1L (ALK in lung cancer trial of brigatinib in first-line), a randomised phase 3 trial of brigatinib (BRG) versus crizotinib (CRZ) in tyrosine kinase inhibitor (TKI)-naive patients (pts) with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC)."	Journal of Clinical Oncology 35 (15 Supplement 1).
	Camidge, R., Kim, H. R., Ahn, M. et al. 2018. "Brigatinib vs Crizotinib in Patients With ALK Inhibitor-Naive Advanced ALK-positive NSCLC: First Report of a Phase 3 Trial (ALTA-1L)."	Journal of Thoracic Oncology 13 (10 Supplement):S184-S185.
	Camidge, D. R., Kim, H. R., Ahn, M. J. et al. 2018. "Brigatinib versus crizotinib in ALK-positive non-small-cell lung cancer."	New England Journal of Medicine 379 (21):2027-2039.
Study 201-ALTA	A Randomised Phase 2 Study of AP26113 in Patients with ALK-positive, Non-small Cell Lung Cancer (NSCLC) Previously Treated with Crizotinib. Clinical Study Report	21 December 2016
	Lenderking, W. R., Speck, R. M., Huang, J. T. et al. 2017. "Evaluating clinically meaningful change of the EORTC QLQ-C30 in patients with NSCLC."	Value in Health 20 (5):A120.
	Langer, C. J., Huang, H., Huang, J. et al. 2017. "Patient-reported outcomes and quality of life in ALTA: The randomised phase 2 study of brigatinib (BRG) in advanced ALK-positive non-small cell lung cancer (NSCLC)."	Journal of Clinical Oncology 35 (15 Supplement 1).
	Langer, C., Huang, H., Reichmann, W. et al. 2017. "Overall survival (OS) after disease progression (PD) on brigatinib in patients with crizotinib-refractory ALK-positive NSCLC in ALTA."	Journal of Thoracic Oncology 12 (11 Supplement 2):S1893-S1894.
	Kim, D. W., Tiseo, M., Ahn, M. J. et al. 2017. "Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: A randomised, multicenter phase II trial."	Journal of Clinical Oncology 35 (22):2490-2498.
	Kawata, A. K., Lenderking, W. R., Eseyin, O. R. et al. 2018. "Converting eortc QLQ-c30 scores to EQ-5D utility scores in the brigatinib ALTA study."	Value in Health 21 (Supplement 1):S210.
	Camidge, D. R., Ahn, M., Reckamp, K. et al. 2017. "Hypertension with brigatinib: Experience in ALTA, a randomised phase 2 trial in crizotinib-refractory ALK-positive NSCLC."	Journal of Thoracic Oncology 12 (11 Supplement 2): S1893.
	Ou, S. H. I., Tiseo, M., Camidge, R. et al. 2017. "Intracranial efficacy of brigatinib (BRG) in patients (Pts) With crizotinib (CRZ)-refractory anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC) and baseline CNS metastases."	Annals of Oncology 28 (Supplement 5): v480-v481.
	Ou, S. H. I., Tiseo, M., Camidge, D. R. et al. 2017. "Brigatinib (BRG) in patients (pts) with crizotinib (CRZ)-refractory ALK-positive non-small cell lung cancer (NSCLC) and brain metastases in the pivotal randomised phase 2 ALTA trial."	Journal of Clinical Oncology 35 (15 Supplement 1).

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Trial ID	Protocol title/ Publication title	Publication citation
	Kim, D. W., Tiseo, M., Ahn, M. J. et al. 2016. "Brigatinib (BRG) in patients (pts) with crizotinib (CRZ)- refractory ALK-positive non-small cell lung cancer (NSCLC): First report of efficacy and safety from a pivotal randomised phase (ph) 2 trial (ALTA)."	Journal of Clinical Oncology 34 (Supplement 15).
	Huber, R. M., Kim, D. W., Ahn, M. J. et al. 2018. "Brigatinib (BRG) in crizotinib (CRZ)-refractory ALK-positive non-small cell lung cancer (NSCLC): Efficacy updates and exploratory analysis of CNS ORR and overall ORR by baseline (BL) brain lesion status."	Journal of Clinical Oncology 36 (15 Supplement 1).
	Camidge, D. R., Tiseo, M., Ahn, M. et al. 2017. "Depth of target lesion response to brigatinib and its association with outcomes in patients with ALK-positive NSCLC in the ALTA trial."	Journal of Thoracic Oncology 12 (11 Supplement 2): S1892.
	Anonymous. 2018. "Erratum: brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase positive non-small-cell lung cancer: a randomised, multicenter phase II trial (American Society of Clinical Oncology (2017) DOI: 10.1200/JCO.2016.71.5904)."	Journal of clinical oncology 36 (9):931.
	Ahn, M. J., Camidge, D. R., Tiseo, M. et al. 2017. "Brigatinib (BRG) in crizotinib (CRZ)-refractory ALK-positive non-small cell lung cancer (NSCLC): Updates from ALTA, a pivotal randomised phase 2 trial."	Journal of Clinical Oncology 35 (15 Supplement 1).
	Ahn, M., Camidge, D. R., Tiseo, M. et al. 2017. "Brigatinib in crizotinib-refractory ALK-positive NSCLC: Updated efficacy and safety results from ALTA, a randomised phase 2 trial."	Journal of Thoracic Oncology 12 (11 Supplement 2): S1755-S1756.
Alectinib studies		
ALEX	Peters, S., Camidge, D. R., Shaw, A. T. et al. 2017. "Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer."	New England Journal of Medicine 377 (9):829-838.
	Shaw, A. T., Peters, S., Mok, T. et al. 2017. "Alectinib versus crizotinib in treatment-naive advanced ALK-positive non-small cell lung cancer (NSCLC): Primary results of the global phase III ALEX study."	Journal of Clinical Oncology 35 (18 Supplement 1).
	Mok, T. S. K., Peters, S., Camidge, D. R. et al. 2017. "Alectinib (ALC) vs crizotinib (CRZ) in treatment-naive ALK-positive non-small-cell lung cancer (NSCLC): Asian vs non-Asian subgroup analysis of the ALEX study."	Annals of Oncology 28 (Supplement 10):x191.
	Mok, T., Peters, S., Ross Camidge, D. et al. 2017. "Patients with ALK IHC-Positive/FISH-Negative NSCLC benefit from ALK TKI treatment: Response data from the global ALEX trial."	Journal of Thoracic Oncology 12 (11 Supplement 2): S1739-S1740.
	Camidge, D. R., Peters, S., Mok, T. et al. 2018. "Updated efficacy and safety data from the global phase III ALEX study of alectinib (ALC) vs crizotinib (CZ) in untreated advanced ALK-positive NSCLC."	Journal of Clinical Oncology 36 (15 Supplement 1).
	Perol, M., Peters, S., Pavlakis, N. et al. 2018. "Patient-reported outcomes (PROs) in ALEX: A phase III study of alectinib (ALEC) vs crizotinib (CRIS) in non-small-cell lung cancer (NSCLC)."	Journal of Thoracic Oncology 13 (4 Supplement 1): S80-S81.

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Trial ID	Protocol title/ Publication title	Publication citation
ALUR	Wolf, J., Oh, I. J., Mazieres, J. et al. 2016. "ALUR: A phase 3 study of alectinib versus chemotherapy in previously treated ALK-positive non-small cell lung cancer (NSCLC)."	Annals of Oncology 27 (Supplement 6).
	Novello, S., Mazieres, J., Oh, I. J. et al. 2018. "Alectinib versus chemotherapy in crizotinib pretreated anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer: Results from the phase III ALUR study."	Annals of Oncology 29 (6):1409-1416.
	Mazieres, J., Novello, S., De Castro, J. et al. 2017. "Patient-reported outcomes and safety from the phase III ALUR study of alectinib vs chemotherapy in pre-treated ALK-positive NSCLC."	Journal of Thoracic Oncology 12 (11 Supplement 2): S1897.
	De Castro, J., Novello, S., Mazieres, J. et al. 2017. "CNS efficacy results from the phase III ALUR study of alectinib vs chemotherapy in previously treated ALK1 NSCLC."	Annals of Oncology 28 (Supplement 5): v481.

Abbreviations: ALK = anaplastic lymphoma kinase; CNS = central nervous system; EORTC = European Organisation for Research and Treatment of Cancer Research; FISH = fluorescence in situ hybridisation IHC = immunohistochemistry; EQ-5D = EuroQoL 5 dimensions; NSCLC = non-small cell lung cancer; ORR = overall response rate; TKI = tyrosine kinase inhibitor;
Source: Table 2-4, p.22-24 of the submission

6.8 The submission excluded two phase 3 RCTs of alectinib, J-ALEX (JapicCTI-132316; N=207) and ALESIA (NCT02838420; N=187), from the assessment of evidence in the first-line setting:

- J-ALEX was an open-label RCT conducted in Japan to compare alectinib and crizotinib. Patients received alectinib 300 mg twice daily, a lower dose than the 600 mg twice daily that is used outside of Japan. ALESIA was an open-label RCT comparing alectinib with crizotinib at 21 investigational centres in Asia. Both trials assessed PFS as the primary endpoint.
- The submission mainly justified the exclusion of these trials on the basis of limited generalisability to the Australian setting due to being conducted exclusively in Asian centres, and that they reflected ethnicity specific studies as part of the development program for both drugs. In addition, Asian patients represented a significant proportion of patients in the brigatinib trials and those with the proposed condition in Australia. While the lower dosing regimen in J-ALEX was a reasonable basis for its exclusion, exclusion of both trials on the basis of ethnicity was inappropriate.

6.9 The key features of the randomised trials for the first-line setting (ALTA-1L, ALEX) and second line setting (Study 201-ALTA, ALURE) are summarised in the table below.

Table 4: Key features of the included evidence – indirect comparison

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Brigatinib						
ALTA-1L	275	R, OL 11 mths	Low	Treatment naïve ^a	PFS, OS, ORR, iORR, HRQoL	PFS
Study 201-ALTA	222	S, OL 17.9 mths	Low	PD after crizotinib; prior chemotherapy	PFS, OS, ORR, HRQoL	Not used
Alectinib						
ALEX	303	R, OL 27.8 mths	Low	Treatment naïve	PFS, OS, ORR, iORR, HRQoL	PFS
ALUR	107	R, OL 6.5 mths	Low	PD after crizotinib and chemotherapy	PFS, OS, ORR, HRQoL	Not used

HRQoL = health-related quality of life; OL=open label; OS=overall survival; PFS=progression-free survival; iORR = intracranial objective response rate; ORR = objective response rate; R=randomised; S = single arm study;

^a ALTA-1L included patients previously treated with chemotherapy whereas the patient cohort in ALEX was treatment naïve including chemotherapy

Source: Developed during the evaluation

First-line setting

6.10 ALTA-1L was an ongoing study at the time of submission. The clinical data presented for brigatinib were from the first interim analysis of ALTA-1L (data cut-off date of 19 February 2018). The median duration of follow-up in ALTA-1L (11.0 months) was relatively short compared with the available data for ALEX (27.8 months for alectinib). At the time of the February 2018 data cut-off, there were 95/137 (69.3%) patients continuing on brigatinib in ALTA-1L. The data from that study were thus immature with respect to the longer-term assessment of efficacy and safety. The ESC noted that the pre-PBAC response could update the PBAC on the results from this second data cut. In response to the ESC's advice, the second interim analysis from the recent data cut-off (28 June 2019) was presented in the pre-PBAC response.

6.11 The following differences were noted in the baseline characteristics for patients in the studies in the first-line setting:

- Both trials enrolled patients who were naïve to prior TKI treatment. Approximately 26% of patients in each arm of ALTA-1L received prior chemotherapy while patients in ALEX were chemotherapy naïve. As such, the population of ALTA-1L could be considered to be more heavily pre-treated, and this difference may have an impact on the expected effectiveness of treatment, but was unlikely to favour brigatinib in the ITC. Results from ALTA-1L showed that the treatment effect for PFS was improved in patients who received prior chemotherapy. Whether the treatment effect with alectinib would be affected by prior chemotherapy was not addressed in the submission. Therefore, it was unclear whether imbalance in prior chemotherapy would result in bias in favour of brigatinib.

- The proportion of patients with ECOG score 0 in ALTA-1L (43%) was higher than in ALEX (32%, Peter et al 2017). Given that patients having better ECOG score were likely to gain more benefit from the treatment from both trials, this imbalance might bias in favour of brigatinib.
- 6.12 Crossover was not permitted in ALEX but was in ALTA-1L. Crossover from crizotinib to brigatinib was permitted for patients who had experienced objective progression. Of the 138 patients initially randomised to crizotinib, 35 (25%) experienced progression and switched therapy to brigatinib (ALTA-1L CSR). There was no report of patients switching from brigatinib to crizotinib. There were limited baseline characteristics of the crossover patients provided in the submission. However, the impact of crossover was not considered relevant for the main treatment effect in the submission (PFS). This was reasonable.
- 6.13 Continuation of treatment beyond progression was allowed in ALTA-1L and ALEX. However, it was likely to be more restricted in ALEX where only patients with asymptomatic CNS progression were allowed to continue treatment beyond progression. Given that ALTA-1L was still ongoing with relatively short follow-up, the full benefits gained (OS and health-related quality of life; HRQoL) from continuation of treatment beyond progression remain unknown. Results from the second data cut could help to inform this.
- 6.14 PFS was the primary outcome in both ALTA-1L and ALEX, primarily assessed by the IRC in ALTA-1L and by investigators in ALEX, and conversely in either study. The base case PFS outcome used in the submission was from the IRC assessment from both trials, and that the results assessed by either the IRC or investigators within each of the trials were consistent, suggesting a low chance of bias between the methods.
- 6.15 The submission presented a minimum clinically important difference (MCID) for PFS in ALTA-1L and ALEX that was based on results of previous studies. Comparative effectiveness in the submission was mainly based on the statistical approaches from the ITC for (PFS, ORR, and iORR). However, the submission did not pre-specify a non-inferiority margin for these outcomes.

Second-line setting

- 6.16 Study 201-ALTA was an RCT in second line post-crizotinib ALK positive NSCLC patients, which compared two dose groups of brigatinib (90 mg and 180 mg). Only results from the 180 mg dose group (n=110) were presented as relevant for the comparison with alectinib. Similarly, ALUR was an RCT in second line post-crizotinib ALK positive NSCLC patients, which compared alectinib with chemotherapy. Only results from the alectinib dose group (n=72) were presented as relevant for the comparison with brigatinib. The submission thus presented a naïve comparison of single arms from RCTs without a common reference. While evidence of within study relative effects were presented (relative to the 90 mg dose group for brigatinib and relative to

chemotherapy for alectinib) these could not be utilised in forming an indirect comparison of brigatinib with alectinib in the second-line setting.

- 6.17 The following differences were noted in the baseline characteristics for patients in Study 201-ALTA (brigatinib) and ALUR (alectinib) in the second-line setting:
- There were imbalances between patients in the 180 mg arm brigatinib in Study 201-ALTA and alectinib arm in ALUR for sex (58% vs 43% female), race (27.3% vs 6.9% Asian), smoking status (57% vs 49% never smoke). Due to lack of a common reference in these trials, whether these differences would introduce bias was unclear.
 - All patients in ALUR received prior platinum chemotherapy, while only 72.7% of patients in Study 201-ALTA received such treatment. There were no further details of patients who did not receive prior platinum-based chemotherapy in Study 201-ALTA provided by the submission. Prior radiotherapy was higher for Study 201-ALTA study than ALUR (53% vs 35%). Based on results from subgroups analysis from these trials, neither of these factors were likely to be associated with the observed treatment effects, noting that these studies were unlikely to be powered to detect treatment effects in these subgroup analyses.
 - In ALUR, patients with CNS metastases were included if asymptomatic, or symptomatic and ineligible for radiotherapy. In Study 201-ALTA, patients were excluded if they had symptomatic CNS metastases that were neurologically unstable or required an increasing dose of corticosteroids. In terms of symptomatic CNS metastases, ALUR might include more patients with a worse prognosis (based on ineligible for radiotherapy), while Study 201-ALTA might exclude more patients with a worse prognosis (neurologically unstable or required an increasing dose of corticosteroids). However, it was unclear whether this difference would introduce bias in favour of brigatinib.
- 6.18 There was also a difference in the primary outcome measures between Study 201-ALTA and ALUR. PFS by investigator assessment was the primary outcome in ALUR but a secondary outcome in Study 201-ALTA. In both trials, PFS was assessed by IRC and investigators. The main results presented in the submission and used as the basis to compare brigatinib with alectinib in the second-line setting were from the IRC assessment of PFS from both trials.
- 6.19 The median duration of follow-up in Study 201-ALTA (31 May 2016 data cut-off: 11 months, 1 August 2017 data cut-off: 17.9 months) was longer than in ALUR (6.5 months). There was a significant difference in duration of treatment between brigatinib and alectinib. Apart from longer PFS time for brigatinib than alectinib, a longer duration of treatment might be partly explained by more patients receiving treatment beyond progression of disease in Study 201-ALTA for brigatinib (25/110; 23%) than in ALUR for alectinib (4/72; 5.5%, Novello et al 2018).

Comparative effectiveness

First-line setting

6.20 A summary of the PFS results for ALTA-1L and ALEX is presented in Table 5, with the corresponding Kaplan-Meier (KM) curves in Figure 1 and Figure 2. Both trials demonstrated a statistically significantly higher PFS for brigatinib and alectinib compared with crizotinib. There was a small numerical difference in the HR for PFS between the trials, but the confidence intervals (CIs) overlapped. The ESC noted that the 12-month PFS rates estimated from KM extrapolation for brigatinib in ALTA-1 and alectinib in ALEX were comparable at 68.5% and 68.4% respectively, but the rates in the crizotinib arms were 40.3% and 48.7% respectively. The ESC also noted that follow-up in ALTA-1L based on the first data cut were particularly immature, such that 69.3% of patients in the brigatinib arm remained on treatment.

Table 5: Results of PFS across the trials: time-to-event data

Trial	Studied intervention		Comparator (crizotinib)		Dif. in median	P value (log rank test)	Hazard ratio (95% CI)	Assessor
	n/N with event (%)	Median time ^c to event (95% CI)	n/N with event (%)	Median time to event (95% CI)				
ALTA-1L (brigatinib)	36/137 (26.3)	NE	63/138 (45.7)	9.76 (9.03, 12.88)	NE	0.0007	0.49 (0.33, 0.74)	IRC
ALTA-1L (brigatinib)	36/137 (26.3)	NE	67/138 (48.6)	9.23 (7.39, 12.94)	NE	0.0001	0.45 (0.30, 0.68)	INV
ALEX ^a (alectinib)	62/152 (41)	NR (17.7, NE)	102/151 (68)	11.1 (9.1, 13.1)	NE	<0.001	0.47 (0.34, 0.65)	INV
ALEX ^a (alectinib)	NR	25.7 (19.9, NE)	NR	10.4 (7.7, 14.6)	15.3	<0.001	0.50 (0.36, 0.70)	IRC
ALEX ^b (alectinib)	72/152 (47.4)	34.8 (17.7, NE)	116/151 (76.8)	10.9 (9.1, 12.9)	23.9	NR	0.43 (0.32, 0.58)	INV

Abbreviations: CI = confidence interval; Dif = difference; INV = investigator; IRC = independent review committee; n = number of participants with event; N = total participants in group; NE = not estimable; NR = not reported; PFS = progression free survival

CI = confidence interval; n = number of participants reporting data; N = total participants in group

^a 1 January 2017 cut-off

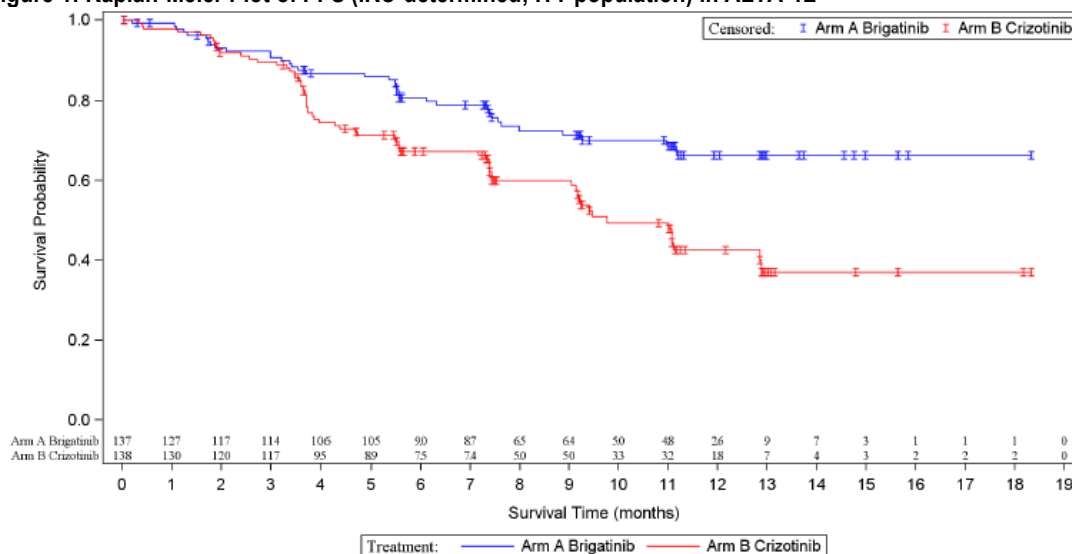
^b 1 December 2017 cut-off, data were sought from the submission and Camidge et al 2019 (italics) by the evaluators.

^c a month is a unit of measurement of time

Note: Text in bold indicate statically significant results; Number in italics indicate values extracted during evaluation

Source: Table 2-19, p.66; Table 2-20, p.67; Table 2-28, p.81; Table 2-72, p.131 of the submission.

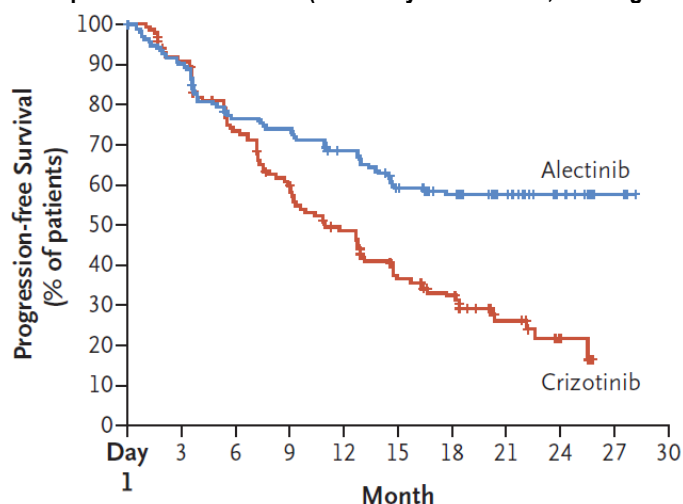
Figure 1: Kaplan-Meier Plot of PFS (IRC-determined; ITT population) in ALTA-1L



Abbreviations: ITT = intention to treat; PFS = progression free survival

Source: Figure 2-8, p.66 of the submission

Figure 2: Kaplan-Meier Plot of PFS (1 January 2017 cut-off; investigators-determined; ITT population) in ALEX



No. at Risk

Alectinib	152	135	113	109	97	81	67	35	15	3
Crizotinib	151	132	104	84	65	46	35	16	5	

Abbreviations: ITT = intention to treat; PFS = progression free survival

Source: Figure 2-17, p.81 of the submission

6.21 A summary of the OS results for ALTA-1L and ALEX is presented in Table 6. The trials showed a non-significant treatment benefit for brigatinib and alectinib respectively, relative to crizotinib, in term of OS. However, the point difference of the treatment effect for OS was more favourable for alectinib. While the CI for the HR on OS overlapped considerably, they were tighter for alectinib likely resulting from a longer duration of follow-up. Nevertheless, the OS data from both trials were immature, as

median OS was not reached in either trial. Comparison of the OS outcomes in the trials were likely to be confounded by differences in clinical practice in the trials including crossover (only in ALTA-1L), treatment beyond progression and the types of treatment used after progression. However, limited data regarding these events were provided by the submission.

Table 6: Results of OS across the trials: time-to-event data

Trial	Studied intervention		Comparator (crizotinib)		Difference in median	P value (log rank test)	Hazard ratio (95% CI)
	n/N with event (%)	Median time to event (95% CI)	n/N with event (%)	Median time to event (95% CI)			
ALTA-1L (briga)	17/137 (12.4)	NE	17/138 (12.3)	NE	NE	0.9611	0.983 (0.50, 1.93)
ALEX ^a (alect)	40/152 (26)	NE	35/151 (23)	NE	NE	NR	0.76 (0.48, 1.20)
ALEX ^b (alect)	43/152 (28.3)	NE	48/151 (31.8)	NE	NE	NR	0.76 (0.50, 1.15)

Abbreviations: CI = confidence interval; n = number of participants with event; N = total participants in group; NE = not estimable; NR = not reported

Notes: Numbers in italics indicate values extracted during evaluation

^a 1 January 2017 cut-off

^b 1 December 2017 cut-off, data were sought from the submission and Camidge et al 2019 (italic) by the evaluators.

Source: Table 2-24, p.73 of the submission.

- 6.22 Results for HRQoL in ALTA-1L showed a clinically meaningful improvement from baseline was observed with both brigatinib (from Cycle 5) and crizotinib (from Cycle 6). The way the submission presented the results of HRQoL by reporting number of cycles showing improvement in HRQoL rather than reporting an average HRQoL score per health state (e.g. progression free or progressed disease) might be less meaningful for decision making and made it more difficult to compare the results with HRQoL in ALEX.
- 6.23 The results of the indirect comparison of PFS, OS, ORR, and iORR between brigatinib and alectinib for the first line setting are presented in Table 7. A comparison of outcomes for HRQoL was not presented, which was appropriate.

Table 7: Results of the indirect comparison for PFS, OS, ORR, and iORR

PFS (IRC)		Studied intervention n/N (%)	Common reference n/N (%)	Absolute difference	HR (95% CI)	
ALTA-1L	Progressed	36/137 (26.3)	63/138 (45.7)	19.4%	-	
	Median months PFS	NE	9.76 (9.03, 12.88)	NE	0.49 (0.33, 0.74)	
ALEX	Progressed	NR	NR	NE	-	
	Median months PFS	25.7 (19.9, NE)	10.4 (7.7, 14.6)	15.3	0.50 (0.36, 0.70)	
Indirect estimate of relative treatment effect					0.98 (0.58, 1.66)	
PFS (INV)		Proposed medicine n/N (%)	Common reference n/N (%)	Absolute difference	HR (95% CI)	
ALTA-1L	Progressed	36/137 (26.3)	67/138 (48.6)	22.3%	-	
	Median months PFS	NE	9.23 (7.39, 12.94)	NE	0.45 (0.30, 0.68)	
ALEX ^a	Progressed	72/152 (47.7)	116/151 (76.8)	29.1%	-	
	Median months PFS	34.8 (17.7, NE)	10.9 (9.1, 12.9)	23.9	0.43 (0.34, 0.58)	
Indirect estimate of relative treatment effect					1.06 (0.64, 1.75)	
OS		Proposed medicine n/N (%)	Common reference n/N (%)	Absolute difference	HR (95% CI)	
ALTA-1L	Death	17/137 (12.4)	17/138 (12.3)	0.1%	-	
	Median month OS	NE	NE	NE	0.98 (0.50, 1.93)	
ALEX	Death	43/152 (28.3)	48/151 (31.8)	-3.5%	-	
	Median month OS	NR	NR	NE	0.76 (0.50, 1.15)	
Indirect estimate of relative treatment effect ^b					1.29 (0.58, 2.85)	
ORR (INV)		Proposed medicine n/N (%)	Common reference n/N (%)	Absolute difference	OR (95% CI)	RR (95% CI)
ALTA-1L		104/137 (75.9)	91/138 (65.9)	10%	1.62 (0.95, 2.75)	1.15 (0.99, 1.34)
ALEX		126/152 (82.9)	114/151 (75.4)	7.5%	1.57 (0.90, 2.76)	1.10 (0.98, 1.23)
Indirect estimate of relative treatment effect					1.03 (0.48, 2.23)	1.05 (0.87, 1.26)
iORR (IRC)		Proposed medicine n/N (%)	Common reference n/N (%)	Absolute difference	OR (95% CI)	RR (95% CI)
ALTA-1L		29/43 (67.4)	8/47 (17.0)	50.4%	10.10 (3.74, 27.25)	3.96 (2.04, 7.70)
ALEX		38/64 (59)	15/58 (26)	33%	4.19 (1.94, 9.06)	2.30 (1.42, 3.71)
Indirect estimate of relative treatment effect					2.41 (0.69, 8.47)	1.72 (0.76, 3.91)

Abbreviations: CI = confidence interval; HR = hazard ratio; IRC = blinded independent committee; PFS = progression free survival; PR = partial response; iORR = intracranial objective response rate; n = number of participants with event; N = total participants in group; NE = not estimable; NR = not reported; OR = odds ratio; ORR = objective response rate; OS = overall survival; RR = relative risk ratio

^a 1 December 2017 cut-off, data were sought from the submission and Camidge et al 2019 (italic) by the evaluators.

^b Estimated during the evaluation.

Note: Text in bold indicate statically significant results; Number in italics indicate values added during evaluation; Indirect estimate of relative treatment effect below 1 favours brigatinib.

Source: Table 2-72, p.131-132 of the submission.

- 6.24 The results of the ITC showed there was no significant difference in treatment effects for PFS, ORR, and iORR between brigatinib and alectinib. The ESC noted the results of the crizotinib arm of the ALTA-1L trial were poorer than in the ALEX trial (e.g. 48.6% vs 76.8% for PFS (INV); 65.9% vs 75.4% for ORR (INV); 17% vs 26% for iORR (IRC)). These differences in the common reference arm contributed to uncertainty in assessing any differential treatment effects of brigatinib and alectinib.
- 6.25 The submission did not undertake the ITC for OS on the basis that the data for OS were immature, particularly for ALTA-1L, and median OS had not been reached in any treatment arm across the two trials.
- 6.26 The submission excluded two trials (J-ALEX and ALESIA) with inadequate justification. In general, clinical outcomes in J-ALEX and ALESIA were consistent with those from ALEX. Compared to crizotinib, the magnitude of PFS treatment effect for alectinib in J-ALEX and ALESIA was numerically greater than brigatinib for both the IRC or investigator assessments. A sensitivity analysis was performed during the evaluation for the ITC in which it included the data for alectinib from J-ALEX and ALESIA. The results from this analysis did not alter the conclusion of non-inferiority presented by the submission’s analysis.
- 6.27 The PBAC noted that the second interim analysis (IA2) for brigatinib from the clinical data of ALTA-1L (data cut-off date of 28th June 2019) was presented in the pre-PBAC response but the results from the IA2 were not independently evaluated for consideration by the PBAC.

Second-line setting

- 6.28 A summary of the results for the second-line setting and the subsequent naïve comparison between brigatinib and alectinib is presented in Table 8.

Table 8: Naïve comparison between Study 201-ALTA (brigatinib) and ALUR (alectinib)

Outcome	180 mg brigatinib	Alectinib	Absolute difference
PFS (IRC)			
Progressed	NR	28/72 (39)	NE
Median months PFS	16.7	7.1	9.6 months
PFS (INV)			
Progressed	NR	25/72 (33)	NE
Median months PFS	15.6	9.6	6 months
OS			
Death	32/110 (29)	NR (22)	7%
Median months OS	27.6	12.6	15 months
ORR (IRC)	60/110 (54.5)	26/72 (36.1)	18.4%
ORR (INV)	61/110 (55.5)	27/72 (37.5)	18%
iORR (IRC)	22/73 (30)	31/74 (42)	12%

Abbreviations: CI = confidence interval; HR = hazard ratio; iORR = intracranial objective response rate; IRC = blinded independent committee; n = number of participants with event; N = total participants in group; NA = not applicable; NE = not estimable; NR = not reported; PFS = progression free survival; OR = odd ratio; ORR objective response rate; RR = relative risk

Source: Table 2-77, p.136 of the submission.

- 6.29 Both median PFS and median OS were longer for brigatinib compared with alectinib. While it appears reasonable to claim that brigatinib provided PFS and OS outcomes at least of a similar magnitude compared with alectinib in the second-line setting, this comparison was not informed by a common reference. The submission did not provide an explanation of the apparent differences in the magnitude of PFS and OS, particularly given the claim of non-inferiority. It was possible that these differences could have arisen due to differences in clinical practice or baseline characteristics of patients across the trials. The PSCR accepted that without a common reference arm, interpretation of these relative survival outcomes is difficult. However, it argued that despite some noted demographic differences, subjects enrolled in the Study 201-ALTA and ALUR trials were well matched on key baseline disease characteristics – ECOG status, histopathology, disease staging, and prior exposure to crizotinib (protocol mandated). Moreover, it suggested that the first-line evidence reinforced a similar trend in survival and tolerability. Nonetheless, the ESC considered that the results should be interpreted with caution given differences in patient demographics and duration of follow-up between the trials.

Comparative harms

First-line setting

- 6.30 A summary of the corrected results from the ITC for safety for the first-line setting is presented in Table 9. The PSCR noted that the submission included errors in the treatment emergent adverse event (TEAE) rates, and these were repeated during the evaluation.

Table 9: Corrected ITC Safety results in ALTA-1L and ALEX

Outcome	ALTA-1L ^c		OR/RD (95% CI) ^d	ALEX		OR/RD (95% CI) ^d	ITC OR (95% CI) ^d
	Brigatini b (N=136)	Crizotini b (N=137)		Alectinib (N=152)	Crizotini b (N=151)		
Grade ≥3	83 (61.0)	76 (55.5)	1.26 (0.78, 2.04)	63 (41)	70 (50)	0.75 (0.46, 1.22)	1.68 (0.80, 3.51)
Patients with Serious AE	34 (25.0)	45 (32.8)	0.68 (0.40, 1.15)	43 (28.0)	44 (29.0)	0.96 (0.58, 1.58)	0.71 (0.34, 1.47)
Leading to study drug discontinuation	16 (11.8)	12 (8.8)	1.39 (0.63, 3.06)	17 (11.0)	19 (13.0)	0.87 (0.44, 1.76)	1.60 (0.56, 4.57)
Leading to dose reduction	39 (28.7)	29 (21.2)	1.50 (0.86, 2.60)	24 (16.0)	31 (21.0)	0.73 (0.40, 1.31)	2.05 (0.91, 4.62) ^b
Leading to dose interruption	72 (52.9)	58 (42.3)	1.53 (0.95, 2.47)	29 (19.0)	38 (25.0)	0.70 (0.41, 1.21)	2.19 (1.06, 4.50)
Any grade AE							
Nausea	36 (26.5)	77 (56.2)	0.28 (0.17, 0.47)	21 (14.0)	72 (48.0)	0.18 (0.10, 0.31)	1.56 (0.73, 3.33)
Diarrhoea	67 (49.3)	75 (54.7)	0.80 (0.50, 1.29)	18 (12.0)	68 (45.0)	0.16 (0.09, 0.29)	5.00 (2.39, 10.46)
Vomiting	25 (18.4)	54 (39.4)	0.35 (0.20, 0.60)	11 (7.0)	58 (38.0)	0.13 (0.06, 0.25)	2.69 (1.09, 6.63)
ALT increased	26 (19.1)	44 (32.1)	0.50 (0.29, 0.87)	23 (15.0)	45 (30.0)	0.42 (0.24, 0.74)	1.19 (0.54, 2.61)
AST increased	31 (22.8)	34 (24.8)	0.89 (0.51, 1.56)	21 (14.0)	37 (25.0)	0.49 (0.27, 0.89)	1.82 (0.80, 4.11)
Blood bilirubin increased	2 (1.5)	3 (2.2)	0.67 (0.11, 4.05)	23 (15)	3 (2)	8.80 (2.58, 29.98)	0.08 (0.01, 0.67)
Dizziness	13 (9.6)	21 (15.3)	0.58 (0.28, 1.22)	12 (8.0)	21 (14.0)	0.53 (0.25, 1.12)	1.09 (0.38, 3.13)
Dysgeusia	6 (4.4)	26 (19.0)	0.20 (0.08, 0.50)	4 (3.0)	29 (19.0)	0.11 (0.04, 0.33)	1.73 (0.42, 7.12)
Visual impairment	0	22 (16.1)	-0.16 (-0.22, -0.10)^a	2 (1.0)	18 (12.0)	-0.11 (-0.16, -0.05)^a	NE
Photopsia	1 (0.7)	28 (20.4)	-0.20 (-0.27, -0.13)^a	0	9 (6.0)	-0.06 (-0.10, -0.02)^a	NE
Visual impairment or photopsia ^d	1 (0.7)	50 (36.5)	0.01 (0.01, 0.10)	2 (1.0)	27 (18.0)	0.06 (0.01, 0.26)	0.21 (0.02, 2.41)
Photosensitivity reaction	5 (3.7)	1 (0.7)	5.19 (0.60, 45.03)	8 (5)	1 (1)	8.33 (1.03, 67.47)	0.62 (0.03, 12.59)
Myalgia	8 (5.9)	6 (4.4)	1.36 (0.46, 4.04)	24 (16)	3 (2)	9.25 (2.72, 31.44)	0.15 (0.03, 0.76)
Musculoskeletal pain	5 (3.7)	8 (5.8)	-0.02 (-0.07, 0.03)^a	11 (7)	0	0.07 (0.03, 0.11)^a	NE
Anaemia	5 (3.7)	7 (5.1)	0.71 (0.22, 2.29)	30 (20)	7 (5.0)	5.06 (2.15, 11.92)	0.14 (0.03, 0.60)

Abbreviations: AE = adverse event; CI = confidence interval; N = total participants in group; NE = not estimable; OR = odds ratio

Note: Figure in bold indicate statically significant results; Number in italics indicate values amended since the evaluation.

a Risk difference (95% CI)

b p value < 0.10

c Data presented for ALTA-1L are from the first pre-planned interim analysis, collection through to data cut-off on 19 February 2018.

Additional interim analyses are planned prior to study completion

d Values originally calculated during the evaluation

Source: developed during the evaluation based on Table 2-46, p.105; Table 2.47, p.106; Table 2-52, p.113; Table 2.53, p.114; of the submission; Table 15.3.1.2.1.2 of Study 301 - ALTA-1L End-of-Text Tables; Table S2 Peter et al 2017

6.31 While the follow-up time from ALTA-1L was shorter than for ALEX, there were more types of AEs that were observed in brigatinib than alectinib. This was consistent with the finding that statistically significantly more patients who received brigatinib experienced more dose interruptions/reductions than alectinib patients.

6.32 The results of the ITC for safety indicate that occurrences of diarrhoea and vomiting were statistically significantly higher for brigatinib than alectinib. Patients treated with brigatinib appeared to have significantly fewer myalgia, anaemia, and blood bilirubin increased events than patients treated with alectinib. The ESC noted, however, that these were based on a shorter duration of follow-up for brigatinib.

Second-line setting

6.33 Results from a naïve comparison of AEs between brigatinib versus alectinib in the second-line setting is presented in Table 10.

Table 10: Safety results of brigatinib in Study 201-ALTA versus alectinib in ALUR

	Brigatinib 180 mg (N=110)	Alectinib (N=70)
Patients with AE	110 (100)	54 (77.1)
Grade ≥3	60 (54.5)	19 (27.1)
Patients with Serious AEs	48 (43.6)	13 (18.6)
Study drug discontinuation due to AEs	11 (10)	4 (5.7)
Dose reduction due to AEs	25 (22.7)	3 (4.3)
Dose interruption due to AEs	54 (49.1)	13 (18.6)
Grade ≥3		
Pneumonia	6 (5.5)	2 (2.9)
Treatment emergent AE		
Nausea	47 (42.7)	1 (1.4)
Diarrhoea	43 (39.1)	2 (2.9)
Fatigue	32 (29.1)	4 (5.7)
Dyspnoea	25 (22.7)	6 (8.6)
Constipation	19 (17.3)	13 (18.6)

Abbreviations; AE = adverse event; CI = confidence interval; N = total participants in group

Note: AE data for 180 mg brigatinib were available from Study 201-ALTA for prior data cut-off (31 May 2016) for median follow-up time of 11 months.

Source: Table 12-2, p.129; Table 12-3, p.131; Table 12-5, p.134; Table 12-9, p.141 of Attachment 4a - Study 201 CSR; Table 2-64, 2-65, p.121; Table 2-67, p.122; of the submission; Table S8 Novello et al 2018

6.34 The naïve comparison suggests that in the second-line setting, brigatinib is associated with a higher incidence of AEs, noting that the comparison does not include a common reference. However, a higher incidence of AEs for brigatinib than alectinib in the second-line setting was likely to be impacted by the longer duration of treatment for brigatinib (approximate median of 10.28 months) than alectinib (approximate median of 5 months), which was consistent with the absolute difference observed in PFS outcomes.

Benefits/harms

6.35 The naïve comparison presented in the submission did not allow for a quantitative comparison of the benefits and harms of brigatinib and alectinib. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.36 The submission stated that brigatinib provides at least similar efficacy to alectinib for the key clinical outcomes (ORR, DOR, PFS, OS and HRQoL) and is associated with a different but overall non-inferior safety and tolerability profile to that seen with alectinib and other ALK targeted TKIs.
- 6.37 For the first-line setting, the claim for non-inferiority in terms of PFS was supported by the evidence presented in the submission. The claim of non-inferiority for OS in the first-line setting was not supported by the evidence, noting the immature nature of the data. The ITC suggested that OS outcomes favoured alectinib over brigatinib. However, the comparison of OS outcomes was potentially confounded by indirect nature of the comparison, differences in the duration of follow-up and difference in practice between trials. Similarly, the claim of non-inferior HRQoL was not supported given the lack of comparative data across the trials (ALTA-1L and ALEX).
- 6.38 For the first-line setting, the claim of non-inferiority in safety compared to alectinib was not adequately supported by the evidence; the ITC suggesting that brigatinib may have a worse safety profile compared to alectinib. In addition, patients receiving brigatinib appeared to have higher rates of dose interruption/reduction and discontinuation of drug compared to alectinib. These trends were observed despite the shorter duration of follow-up for brigatinib with a high number of patients still receiving treatment in ALTA-1L compared with ALEX. The ESC noted that ALK-TKIs have different adverse event profiles, making comparisons difficult.
- 6.39 In the second-line setting, the efficacy claims for PFS and OS may have been reasonable, but were based on comparison of single arms from RCTs and were not informed by a common reference. The ESC considered that the claim was not adequately supported by the data presented. Similar to the first-line setting, there was a lack of a meaningful comparative analysis of HRQoL between brigatinib and alectinib.
- 6.40 In the second-line setting, brigatinib appeared to have a worse safety profile compared to alectinib, although the ESC considered that the different safety profiles make the comparison difficult, with or without a common reference arm. Furthermore, the ESC considered that the higher incidence of AEs for brigatinib than alectinib in the second-line setting may also reflect the longer duration of treatment for brigatinib.
- 6.41 The PBAC considered that the claim of non-inferior effectiveness compared with alectinib in the first-line setting was reasonable. The PBAC considered that the claim of non-inferior effectiveness compared with alectinib in the second-line setting was uncertain, however, considered it reasonable to conclude that the effectiveness of brigatinib is also similar to alectinib post-crizotinib therapy.

6.42 The PBAC considered that the safety profile of brigatinib to be different to alectinib, making the comparison difficult, however accepted that there is no substantive difference in safety across the two drugs.

Economic analysis

6.43 The submission presented a CMA comparing brigatinib to alectinib. The components and assumptions of the CMA are presented in Table 11.

Table 11: Summary of key components and assumptions of the cost-minimisation analysis

Component	Summary
Therapeutic claim: effectiveness	Based on evidence presented in the submission, effectiveness is assumed to be non-inferior
Therapeutic claim: safety	Based on evidence presented in the submission, safety is assumed to be non-inferior, with slightly different profile of adverse events
Evidence base	Treatment naïve patients: Indirect comparison based on ALTA-1L and ALEX Crizotinib treated patients: Naïve indirect comparison based on Study 201-ALTA and ALUR
Equi-effective doses	Brigatinib █████ mg daily = Alectinib 1,147.20 mg daily (divided dose)
Direct medicine costs	Alectinib Approved Ex-Manufacturer Price (AEMP) (224 x 150 mg) = \$6,653.08
Other costs or cost offsets	None included

Abbreviations: AEMP = approved ex-manufacturer price; mg = milligram

Source: Table 3-1, p154 of the submission

6.44 The equi-effective doses proposed in the submission were estimated assuming that brigatinib █████ mg/day is equivalent to alectinib 1147.2 mg/day based on the relative dose intensity (RDI) reported in ALTA-1L (brigatinib RDI, █████%) and ALEX (alectinib RDI, 95.6%). The estimates of the equi-effective doses were not directly incorporated into the CMA as the submission applied the RDI for alectinib to calculate the cost-minimised price of brigatinib. The calculations applied in the submission were based on use in the first-line setting only.

6.45 The submission also did not apply the treatment duration for brigatinib and alectinib in its calculation of the equi-effective doses. The submission noted that the median treatment duration in the brigatinib trial (ALTA-1L) and alectinib trial (ALEX) was censored due to the end of follow-up and argued that this did not provide an appropriate basis for comparison between the trials. The submission proposed using Kaplan-Meier estimates of PFS as a proxy for treatment duration. This was not reasonable given that Kaplan-Meier estimates of PFS were also immature in ALTA-1L. Regardless, the submission did not use PFS as a proxy for treatment duration, but assumed non-inferiority of PFS and thus did not adjust drug exposure for duration. However, evidence from the comparison of brigatinib to alectinib in the second-line setting suggested a significant difference in median treatment duration (17.25 months for brigatinib in Study 201 and 5 months for alectinib in ALUR).

6.46 The CMA applied the RDI directly from ALEX for alectinib (95.60%), while the RDI for brigatinib (ALTA-1L) was not applied, which was not appropriate. The PSCR argued that no adjustments for the RDI of brigatinib were made in the CMA given the multiple

dose forms available and flat pricing structure proposed across these forms. It argued that titrations of brigatinib dosing would be reflected in the distribution of packs dispensed, rather than result in an increase in the number of days of treatment dispensed per pack.

6.47 The submission estimated a cost-minimised AEMP published price for brigatinib of \$ [REDACTED] per pack (Table 12), calculated based on the total cost per day of treatment for alectinib. The ESC has previously considered that cost-minimisation analysis based on the cost per day assumes that the mean duration of treatment between the drug and its comparator was the same (paragraph 6.51, alectinib PSD, July 2017). Data from ALTA-1L were immature with respect to follow-up, and data from the second-line setting suggested that the duration of therapy for brigatinib may have been substantially longer than that for alectinib. Whilst there were transitivity issues between the trials in the second-line setting due to differences in the patient population and study conduct, the ESC remained of the view that it was not reasonable to assume the same mean duration of treatment for both drugs in the CMA.

6.48 The submission based its CMA on the comparison of brigatinib with alectinib. The initial listing for alectinib assumed a dose equivalence for alectinib 600 mg BID with ceritinib 750 mg QD. However, ceritinib dosing has been revised to 450 mg QD. The impact on the resulting published treatment cost per day is presented in Table 12.

Table 12: Results of the cost-minimisation analysis

Name, restriction, manner of administration, form	Maximum quantity (units)	Days of treatment per pack	DPMQ (published)	AEMP (published)	RDI	Treatment cost (daily) (AEMP)	Dose regimen assumption
Alectinib 150 mg capsule	224	28	\$6,805.20	\$6,653.08	95.60%	\$227.16	600 mg BID
Brigatinib 180 mg tablet	180	28	\$ [REDACTED]	\$ [REDACTED]	NA	\$ [REDACTED]	180 mg QD
Ceritinib 150 mg capsule	150	50	\$7,280.42	\$7,128.30	100%	\$142.57	450 mg QD
Ceritinib 150 mg capsule	150	30	\$7,280.42	\$7,128.30	100% ^a	\$237.61	750 mg QD

Abbreviations: AEMP = approved ex-manufacturer price; BID = twice daily; DPMQ = dispensed price per maximum quantity; mg = milligram; RDI = relative dose intensity; QD = once daily

Note: Number in italics indicate values calculated during evaluation

^a RDI in ASCEND-5

Source: Table 3-3, p156 of the submission Ceritinib DPMQ, URL: <http://www.pbs.gov.au/medicine/item/11056X>

6.49 The submission did not include additional costs and /or cost offsets associated with use of brigatinib compared with alectinib, and assumed the inclusion of brigatinib within MBS Item 73341 was not expected to alter the utilisation of the service.

Drug cost/patient/course

- 6.50 Applying the submission's prices, the cost/patient/course for brigatinib in the first-line setting was estimated to be \$ [REDACTED] (using published prices). This was calculated using the proposed dispensed price of brigatinib of \$ [REDACTED], assuming each 28 day supply provided for [REDACTED] days' treatment (allowing for an RDI of [REDACTED]%) and assuming a mean treatment duration of [REDACTED] months (ALTA-1L). Data in ALTA-1L were immature and therefore the total cost of treatment in the first-line setting is likely to be underestimated. The ESC noted that the pre-PBAC response could provide an update on treatment duration in ALTA-1L based on the second data cut-off.
- 6.51 The cost/patient/course for brigatinib in the second-line setting was estimated at \$ [REDACTED] (using published prices). This was calculated using the proposed dispensed price of brigatinib of \$ [REDACTED] for 28 days of supply assuming a mean treatment duration of 16.36 months. Table 13 presents the results of re-analysis of the cost/patient/course. The treatment duration for brigatinib was longer in the second-line-setting (median 17.25 months) than in the first-line setting (median 9.22 months), reflecting the shorter follow-up for brigatinib in the first-line setting (median 11 months).

Table 13: Drug cost per patient for proposed and comparator drugs

	Brigatinib		Alectinib	
	CMA	Financial estimates	CMA	Financial estimates
Equi-effective dose (as per submission)	█ mg average daily dose	█ mg average daily dose	1147.2 mg average daily dose	600 mg (4x 150 mg) BD
Median duration of treatment (months)	9.22	NA	17.9	NA
Mean duration of treatment (months)	█	18	17.1	18
Cost/patient/month	\$█	\$█	\$6,805	\$6,805
Cost/patient/ Course-1 st line-setting	\$█ ^a	\$█ ^b	\$120,742 ^c	\$133,066 ^d
Cost/patient/ Course-2 nd line-setting	\$█ ^e	NA	\$32,603 ^f	NA

Abbreviations: CMA = cost-minimisation analysis; BD = twice daily; mg = milligram; NA = not available; NR = not reported; QD = once daily.
Notes: Italics indicate values calculated during evaluation

a Estimated during the evaluation using proposed dispensing price of brigatinib of \$█ for █ days' supply, assuming a mean treatment duration of █ months (ALTA-1L) and an RDI of █%.

b Estimated during the evaluation using proposed dispensing price of brigatinib of \$█ for 28 days' supply, assuming a mean treatment duration of 18 months.

c Estimated during the evaluation using proposed dispensing price of alectinib of \$6,805 for 29.29 days' supply, assuming a mean treatment duration of 17.08 months and an RDI of 95.60%.

d Estimated during the evaluation using proposed dispensing price of alectinib of \$6,805 for 28 days' supply, assuming a mean treatment duration of 18 months.

e Estimated during the evaluation using proposed dispensing price of brigatinib of \$█ for 28 days' supply, assuming a mean treatment duration of █ months. Mean treatment duration in second line-treatment setting was estimated based on median treatment duration in second-line setting for brigatinib (Study 201 ALTA, Part B, 2nd data cut off) multiplied by the estimated ratio between mean and median treatment duration reported in second-line treatment setting trial (Study 201 ALTA, Part B 1st data cut-off)

f Estimated during the evaluation using proposed dispensing price of alectinib of \$6,805 for 28 days' supply, assuming a mean treatment duration of 4.4 months. Mean treatment duration in second line-treatment setting was estimated based on median treatment duration in second-line setting for alectinib (ALUR) multiplied by the estimated ratio between mean and median treatment duration reported in second-line treatment setting trial (Study 201 ALTA, Part B 1st data cut-off)

Source: Table 2.13, p.48; Table 2-45, p.104, Table 2-29, p.84; Table 3-1, p154 of the submission; compiled during the evaluation

Estimated PBS usage & financial implications

6.52 This submission was not considered by DUSC.

6.53 The submission adopted a market share approach to estimate the potential utilisation of brigatinib on the PBS/RPBS. In order to derive the estimate of the market size for brigatinib, the submission applied the estimated number of scripts for alectinib, applying a script equivalence of 1:1 between brigatinib and alectinib.

6.54 The mean dose intensity calculated based on the distribution of use of brigatinib prescriptions within the different pack sizes of brigatinib showed the mean dose intensity applied in the financial implications' estimates was lower than the mean dose intensity reported in ALTA-1L (█ mg vs. █ mg, ALTA-1L CSR). However, this

did not impact on the estimated financial implications of listing brigatinib as the submission applied a flat-pricing structure across the packs.

- 6.55 The market share of alectinib was estimated based on 6 months of PBS Statistics (November 2018 to April 2019), adjusted on a pro-rata basis to provide a 12 months equivalent of market share estimates. The estimated ALK inhibitors market growth during the most recent 6 months (November 2018 to April 2019) period was 1%. This was reasonable.
- 6.56 The submission made the following assumptions in estimating substitution within the financial estimates:
- The market growth without brigatinib was limited to underlying population growth, ranging from 1.7% to 1.5% over the forecast period based on ABS-Series B projections. The submission assumed a small increase to overall market that was related to the entry of brigatinib. This was appropriate. The ESC noted that the overall market growth of ALK TKIs appeared to be stable, and considered that additional growth attributed to the introduction of brigatinib would most likely be small. The PSCR noted that in the scenario following brigatinib PBS listing, additional growth was included: █% in Year 1 rising to █% in Year 2 before declining over subsequent years to █% in Year 6. This was reasonable.
 - The uptake rate for brigatinib was assumed to be █% in Year 1 increasing linearly to █% by Year 6. The remaining market share was apportioned across the existing medicines according to the market shares expected for the scenario without brigatinib. This seemed appropriate.
 - The submission assumed that there is no set treatment sequence for the use of ALK inhibitors in NSCLC and excluded use of a single agent only. However, brigatinib was expected to substitute for alectinib given the submission sought a line agnostic listing. The submission assumed there would be substitution of brigatinib for other currently listed ALK-TKIs rather than displacement. The ESC noted that the financial impact would be underestimated if there was a greater substitution for ceritinib 450 mg, as it is a cheaper therapy. The PSCR stated that the submission did consider the displacement of other TKIs, with the provision of an additional growth rate (the █% increase noted above). It also argued that the expected use of brigatinib in the first-line setting will displace alectinib and ceritinib into later therapy lines, but is unlikely to fully displace TKI use into an additional line (i.e. 4th line). The ESC agreed that the impact of displacement would be minimal, given the poor prognosis of NSCLC after second-line therapy. The ESC also noted that the submission did not consider the financial impact of a near market comparator, lorlatinib, if recommended for listing.

- The submission assumed that dose reductions for brigatinib would apply from treatment initiation. This would result in overestimation of the total number of scripts utilised at the reduced dose. However, as the submission applied flat pricing across all pack sizes, this did not impact on the estimated financial implications.

6.57 A summary of the estimated use and financial implications for listing brigatinib is presented in Table 14, based on published prices.

Table 14: Net PBS/RPBS financial implications for listing brigatinib

Published Price	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated volume of brigatinib (scripts)	■	■	■	■	■	■
Cost to Government for PBS (patient co-payments removed)	\$■	\$■	\$■	\$■	\$■	\$■
Cost to Government for RPBS (patient co-payments removed)	\$■	\$■	\$■	\$■	\$■	\$■
Total cost to Government for PBS/RPBS	\$■	\$■	\$■	\$■	\$■	\$■
Cost to Government for PBS substituted medicines (patient co-payments removed)	\$■	\$■	\$■	\$■	\$■	\$■
Cost to Government for RPBS substituted medicines (patient co-payments removed)	\$■	\$■	\$■	\$■	\$■	\$■
Total cost to Government for PBS/RPBS substituted medicines	\$■	\$■	\$■	\$■	\$■	\$■
Net Cost to Government for PBS/RPBS (patient co-payments removed)	-\$■	-\$■	-\$■	-\$■	-\$■	-\$■

Abbreviations: PBS = Pharmaceutical Benefit Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme.
Source: Table 4-13, p173 of the submission

- 6.58 The results of budget impact analysis presented by the submission resulted in a saving to Government of approximately less than \$10 million in Year 1, rising to reductions of less than \$10 million in Year 6 of listing (published prices applied).
- 6.59 The results of estimated use and financial implications for listing brigatinib assuming displacement rather than substitution would have the effect of reducing the cost-offsets claimed by the submission. Assuming that displacement was to occur in half of those patients for whom it was assumed that substitution of brigatinib occurred, the total financial implications of listing brigatinib would be less than \$10 million in Year 1 to less than \$10 million in Year 6 after listing, based on published prices. However, as noted above, the ESC agreed with the PSCR that the impact of displacement was likely to be relatively minimal.
- 6.60 The submission expected no change in MBS item utilisation assuming the eligibility testing, monitoring requirements and AE management of brigatinib were consistent

with those of alectinib and therefore the inclusion of brigatinib within MBS Item 73341 was not expected to alter the utilisation of the service.

Financial Management – Risk Sharing Arrangements

- 6.61 The submission requested a Special Pricing Arrangement for brigatinib and inclusion in a financial risk sharing arrangement if such an arrangement is in place for the already approved medicines: alectinib, crizotinib and ceritinib.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

- 7.1 The PBAC recommended the Authority Required listing of brigatinib as monotherapy for the treatment of patients with locally advanced (Stage IIIB) or metastatic (Stage IV) anaplastic lymphoma kinase (ALK)-positive non-squamous (NS) or not otherwise specified (NOS) non-small cell lung cancer (NSCLC). The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of brigatinib would be acceptable if it were cost-minimised against alectinib.
- 7.2 The PBAC noted that the existing listings for ALK-tyrosine kinase inhibitors (TKI) are line-agnostic and there is a lack of evidence for the optimal sequence of ALK inhibitor therapies in ALK-positive NSCLC and therefore considered that brigatinib should not be precluded from a line-agnostic listing. Further, the PBAC noted that the results from the phase 3 randomised controlled trial (RCT) of brigatinib versus crizotinib (ALTA-1L) in the first-line setting supported that brigatinib is superior in efficacy and safety compared with crizotinib, and that would likely justify the clinical place of brigatinib as first-line therapy. As such, the PBAC considered that the listing of brigatinib would provide an alternative ALK-TKI with intracranial activity and a different profile in terms of safety and tolerability.
- 7.3 The PBAC considered that alectinib was the appropriate main comparator, as it would most likely be replaced if brigatinib was available on the PBS in both the first-line and second-line settings.
- 7.4 The PBAC considered ceritinib was an appropriate supplementary comparator as alectinib was listed on a cost-minimisation basis versus ceritinib. The PBAC noted the recommended dose for ceritinib had changed from 750 mg to 450 mg, based on pharmacokinetic (PK) data but that based on PBS data the lower dose does not yet appear to be used in clinical practice (paragraph 5.4), and there is a lack of long term clinical data at the lower dose.
- 7.5 The submission was on the basis of an indirect treatment comparison (ITC) of brigatinib (ALTA-1L, n=275) and alectinib (ALEX, n=303), using crizotinib as a common reference in the first-line setting and a naïve comparison of single arm studies of brigatinib (Study 201-ALTA, n=222) and alectinib (ALUR, n=107) in the second-line setting. The PBAC considered the comparison of brigatinib and alectinib in the first-

- line setting to be of greater relevance to current practice in ALK-positive NSCLC whereas data from the trials in the second-line setting represented a relatively small subgroup of patients previously treated with crizotinib as first-line therapy, with limited applicability due to the decline in crizotinib utilisation in clinical practice.
- 7.6 For the first-line setting, the PBAC noted the PFS hazard ratio (HR) as the primary outcome for brigatinib was comparable to the PFS HR for alectinib, and considered that the HR was not substantially altered with a longer duration of follow-up for alectinib (28 months) compared with brigatinib (11 months); the PBAC also noted that the 12-month PFS rates estimated from Kaplan-Meier (KM) extrapolation for brigatinib and alectinib were similar. As such, the PBAC considered that a conclusion of non-inferiority in efficacy was supported by the ITC for PFS, but not for OS, largely due to the immature data from both trials. Further, the PBAC noted that the ITC found no significant difference in treatment effects for overall response rate (ORR) and intracranial response between brigatinib and alectinib, which was supportive of non-inferior efficacy for brigatinib relative to alectinib.
- 7.7 The PBAC noted that median PFS and median OS were longer for brigatinib compared with alectinib in the second-line setting but considered the results should be interpreted with caution given that the data presented were based on a naïve comparison of single arm studies without a common reference. Overall, the PBAC considered it was reasonable to conclude that the effectiveness of brigatinib may also be similar to alectinib post-crizotinib therapy.
- 7.8 The PBAC noted the higher rates of treatment discontinuations, interruption and dose reduction with brigatinib compared with alectinib. However, the PBAC noted that all ALK-TKIs have different safety profiles, making the comparison difficult, and accepted that there does not appear to be any substantive difference in safety across the two drugs.
- 7.9 The equi-effective doses proposed in the submission were brigatinib [REDACTED] mg per day and alectinib 1147.2 mg per day, based on the relative dose intensity (RDI) reported in ALTA-1L (brigatinib RDI, [REDACTED]%) and ALEX (alectinib RDI, 95.6%). However, the PBAC noted that the estimates of the equi-effective doses were not directly incorporated into the cost-minimisation analysis (CMA). Instead, the RDI for alectinib but not brigatinib was applied effectively resulting in equi-effective doses of brigatinib 180 mg per day and alectinib 1147.2 mg per day. The PBAC noted the lower RDI for brigatinib compared with alectinib resulted in a higher price for brigatinib and considered that the lower RDI for brigatinib was not adequately supported.
- 7.10 The PBAC noted that the equi-effective doses for brigatinib and alectinib did not incorporate the treatment durations as observed in the trials. The PBAC considered this was appropriate noting the data available for the first line setting supported a similar treatment effect at similar timepoints, and that the data from the brigatinib trial were immature with respect to follow-up to be a basis for accepting a shorter

- duration. In addition, the data available for the second-line setting were less robust than the first-line setting.
- 7.11 The PBAC determined the equi-effective doses to be brigatinib 180 mg daily and alectinib 600 mg twice daily. The PBAC noted ceritinib is also a relevant alternative therapy and that as an improvement in efficacy or reduction in toxicity with brigatinib over ceritinib was not demonstrated for some patients, that brigatinib 180 mg daily should also be no more costly than ceritinib 750 mg daily.
- 7.12 The PBAC considered brigatinib would replace alectinib, and to small degree, ceritinib in both the first-line and second-line settings. The PBAC considered the market growth due to listing another TKI would be minimal, and hence the financial estimates as presented in the submission with no additional PBS expenditure as a result of listing brigatinib to be reasonable.
- 7.13 The PBAC noted that there is currently a risk sharing arrangement for alectinib, and that it would be appropriate for brigatinib to be subject to the same risk sharing arrangements as alectinib.
- 7.14 The PBAC noted that the requested listing was broader than the registered TGA indication (post-crizotinib therapy) but the requested line-agnostic listing was reasonable given the similarity of the available clinical data for brigatinib and alectinib at the time of PBAC consideration. The submission requested the same restrictions as for alectinib without the need for grandfathering provisions, which was considered to be appropriate.
- 7.15 The PBAC noted that the brigatinib PI provided a special warning and precaution for use regarding brigatinib-associated severe pulmonary adverse events (AEs), and considered that education would be required for prescribers and consumers that the recommended starting dose is 90 mg once daily and patients should be monitored for and instructed to report any new or worsening respiratory symptoms, particularly during the first week of initiating brigatinib, as most pulmonary AEs were observed within the first 7 days of treatment.
- 7.16 The PBAC noted that the requested maximum quantity and repeats were the same as for alectinib for continuing treatment, and advised that this restriction should be consistent across all ALK inhibitors.
- 7.17 The PBAC advised that under Section 101(3BA) of the *National Health Act 1953* brigatinib should not be treated as interchangeable with any other drugs on an individual patient basis.
- 7.18 The PBAC advised that brigatinib is not suitable for prescribing by nurse practitioners.
- 7.19 The PBAC recommended that the Early Supply Rule should not apply.
- 7.20 The PBAC noted that its recommendation was on a cost-minimisation basis and advised that, because brigatinib is not expected to provide a substantial and clinically

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relevant improvement in efficacy, or reduction of toxicity, over alectinib, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by *the National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met.

7.21 The PBAC advised that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer
BRIGATINIB 90 mg tablet [7] (&) 180 mg tablet [21], 1 pack	1	0	Alunbrig® Takeda Pharmaceuticals Australia Pty Ltd

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition:	non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Initial treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Clinical criteria:	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.
Population criteria:	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.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

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Caution:	Careful monitoring of patients is required due to risk of developing pulmonary adverse events observed in patients within the first seven days of treatment with brigatinib. Patients must be instructed to report any new or worsening respiratory symptoms.
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Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Name and Manufacturer	
BRIGATINIB			Alunbrig®	Takeda Pharmaceuticals Australia Pty Ltd
30 mg tablets, 28	4	1		
90 mg tablets, 28	1	1		
180 mg tablets, 28	1	1		

Category / Program:	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Severity:	Stage IIIB (locally advanced) or Stage IV (metastatic)
Condition:	non-small cell lung cancer (NSCLC)
PBS Indication:	Stage IIIB (locally advanced) or Stage IV (metastatic) non-small cell lung cancer (NSCLC)
Treatment phase:	Continuing treatment
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required – In Writing <input checked="" type="checkbox"/> Authority Required – Telephone/Electronic/Emergency <input type="checkbox"/> Streamlined
Clinical criteria:	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.
Administrative Advice:	No increase in the maximum quantity or number of units may be authorised. No increase in the maximum number of repeats may be authorised. Special Pricing Arrangements apply.

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances

in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Takeda Australia welcomes the PBAC's decision to recommend brigatinib for the treatment of locally advanced or metastatic ALK positive non-small cell lung cancer. Takeda believes brigatinib provides an effective treatment option for this high need patient population, and will be an important addition to the clinical management of ALK positive NSCLC in Australia. Takeda also wishes to thank those patients, clinicians, and organisations who took time to submit comments during the PBAC process.