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HEALTH TECHNOLOGY ASSESSMENT REPORT

ANAPLASTIC LYMPHOMA KINASE (ALK) TYROSINE KINASE INHIBITOR (TKI) FOR NON-SMALL CELL LUNG CANCER

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
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IPT Mark
HTA Report
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Published by:

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Complex E, Precinct 1
Federal Government Administrative Centre
62590, Putrajaya, Malaysia
Tel: 603 8883 1229
Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

ISBN:

e-ISBN:

This HTA report was endorsed in the HTA & CPG Council Meeting 2/2022 (November 2022).

SUGGESTED CITATION: Roza S, Balqis AG, Sit Wai L and Izzuna MMG. Anaplastic lymphoma kinase (ALK) Tyrosine Kinase Inhibitor (TKI) for Non-small cell lung cancer: Health Technology Assessment. Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2022. 61 p. Report No.: 04/2022. ISBN:

DISCLOSURE: The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

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ACKNOWLEDGEMENT

The authors of this Health Technology Assessment Report would like to express their gratitude and appreciation to the following for their contribution and assistance:

- Health Technology Assessment and Clinical Practice Guidelines Council.
- Technical Advisory Committee for Health Technology Assessment.
- Technical Advisory Committee for Health Technology Economic Evaluation.
- Madam Ku Nurhasni Ku Abdul Rahim for her technical input in reviewing the economic evaluation part and Madam Zamilah Mat Jusoh for her assistance in the retrieval of evidence.

EXECUTIVE SUMMARY

Background

Worldwide, lung cancer is the leading cause of cancer-related death. The highest lung cancer incidence (59.6%) and mortality (61.9%) were reported in Asia. In Malaysia, lung cancer is the third most common cancer, while in the 25-59 age group it is the second most common. Although majority of cases were detected in current or ex-smokers, increasingly patients with minimal or no smoking history were being diagnosed. Nearly 90% of lung cancer cases in Malaysia were diagnosed at an advanced stage. The 5-year observed survival rate was 9.0%. Median overall survival was 18 weeks for patients presented with either stage III or IV disease without definitive treatment reported in a local study. Approximately 94% of patients with advanced disease were diagnosed with non-small cell lung cancer (NSCLC).The NSCLC accounted for nearly 85% of all lung cancer cases. Anaplastic Lymphoma Kinase (ALK) positive NSCLC represents approximately 4 to 5% of all NSCLC patients in both Caucasian and Asian populations, representing potentially 40,000 new cases worldwide annually. Patients with ALK positive is typically seen in relatively young age, with a never or light smoking history. These patients have a high risk of developing brain metastases, as observed in at least 20% of cases at diagnosis. These patients harbour a genetic rearrangement in the ALK gene, resulting in a novel fusion oncogene *EML4-ALK* that promote tumour growth and survival. The management of advanced NSCLC has transformed due to improvement in the understanding of molecular drivers of carcinogenesis. The discovery of oncogenes, such as ALK along with the development of therapy targeting these mutations have led to the ability to personalize therapy. The treatment paradigm has evolved from non-specific curative approaches, to the use of therapy targeting particular actionable genetic mutations. Patients with ALK positive have been identified as subgroup of lung cancer patients to gain survival benefit from targeted therapy. The therapeutic landscape of ALK positive NSCLC has led to the introduction of three generations of ALK inhibitors involving different highly potent molecules. Several ALK-inhibitors were registered with National Pharmaceutical Regulatory Agency (NPRA), however they are not available in the MOH formulary. International guidelines recommended testing for ALK mutation in all non-squamous NSCLC. In 2019 the Malaysian guideline on molecular testing for advanced NSCLC patients highlighted ALK, ROS1 rearrangement, EGFR and BRAF mutation as ‘must-test’ biomarkers. However, the high cost of molecular testing and systemic therapy limit the availability of treatment options for many Malaysian population. The review is timely to address the increasing need to provide targeted therapy with better efficacy and lower toxicity in advanced ALK positive NSCLC patients in the country. Therefore, this assessment will evaluate whether it would be effective, safe and cost-effective to use ALK inhibitor in the management of ALK positive advanced NSCLC patients in Malaysia as requested by a Clinical Oncologist from Hospital Kuala Lumpur.

Technical features

The *ALK* gene is located on the short arm of chromosome 2 (2p23), belongs to the insulin receptor superfamily, and encodes for the ALK protein. ALK is a transmembrane tyrosine kinase receptor, which is physiologically expressed in the nervous system during embryogenesis. ALK was originally identified in anaplastic large-cell lymphoma hence the name anaplastic lymphoma kinase. Subsequently, ALK-rearrangement (ALK-R) was identified in the pathogenesis of several cancers, including inflammatory myofibroblastic tumors, diffuse large B-cell lymphoma, esophageal squamous cell and colorectal carcinomas. ALK gene arrangement was discovered in NSCLC (2007). The three types of *ALK* gene mutations are rearrangement (ALK-R), amplification (ALK-A), and point mutation. Most mutations of the *ALK* gene are in the form of translocation with another partner gene leading to a fusion oncogene, which becomes overly expressed in cancers. ALK rearrangements create an oncogenic ALK tyrosine kinase that activates many downstream signaling pathways resulting in increased cell proliferation and survival. More than 19 different ALK fusion partners have been discovered in NSCLC, including EML4, KIF5B, KLC1, and TPR. The most common alteration of ALK is the fusion of ALK gene with the echinoderm microtubule associated protein like -4 (EML4) gene. This gene alteration was resulted from interchromosomal inversion within the short arm of chromosome 2 joining the exons 1-13 of the EML4 gene, to exons 20-29 of ALK gene. NSCLC with positive ALK-EML4 gene fusion is highly sensitive to ALK inhibition by molecules designed to target tyrosine kinase.

The introduction of three generations of ALK TKI involved different highly potent molecules. Crizotinib is the first generation ALK inhibitor with recommended dose of 250 mg twice daily in a 28-day cycle until disease progression or no longer tolerated by the patient. It is a multi-targeted TKI, the first TKI approved by the USFDA for metastatic NSCLC patients with ALK mutation (2011), however almost a third of the patients had developed primary or secondary resistance within one to two years.

Ceritinib is a second-generation ALK TKI which is 20 times as potent as crizotinib, with a therapeutic dose of 450 mg orally once daily. Ceritinib was indicated to ALK-positive patients with disease progression on or intolerance to crizotinib (2014), subsequently indicated as first-line therapy (2017). Ceritinib inhibits the autophosphorylation of ALK, and the molecular targets include IGF-1 R, InsR, and ROS1. Ceritinib inhibits the most common ALK mutations, such as L1196 M, G1269A, I1171T, and S1206Y, which determine resistance to crizotinib.

Alectinib is a highly potent second-generation ALK that has RET (Rearranged during Transfection) gene activity inhibitor, with recommended twice-daily dose of 600 mg.[27] Alectinib is indicated for NSCLC patients with ALK rearrangement who have benefited previously from crizotinib (2015) and subsequently indicated as first-line therapy (2017). It is efficient for patients with crizotinib-resistant ALK mutations.

Brigatinib is a highly potent selective second generation ALK inhibitor, indicated as a first line option for patients with ALK positive NSCLC (2020), with recommended dose of 90mg orally once daily for first seven days then increase to 180mg orally once daily, until disease progression or unacceptable toxicity.

In order to overtake acquired resistance, prolong the control of the disease, and manage CNS disease, other highly potent next-generation ALK TKIs were introduced such as lorlatinib and ensartinib. Lorlatinib is a third-generation ALK- and ROS1-inhibitor, a selective,

brain penetrating ALK TKI, designed to target mutations which drive resistance to crizotinib and next-generation TKIs. Recommended dose is 100 mg once daily, indicated as the first-line therapy for metastatic ALK rearranged NSCLC patients with progressive disease on crizotinib and other ALK inhibitors (2018). Ensartinib displayed activity against MET, Axl, ABL, EPHA2, LTK, ROS1, and SLK genes, created to improve the activity on CNS metastases. Entrectinib is a potent, selective, oral inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK, with the ability to cross the blood - brain barrier.

Policy question

Should targeted therapy (ALK tyrosine kinase inhibitor) be used as a standard treatment option for patients with advanced and metastatic ALK positive NSCLC in the Ministry of Health hospitals?

Objective

i. To assess the comparative effectiveness and safety of ALK tyrosine kinase inhibitors given as monotheraphy to treat patients with advanced and metastatic ALK positive NSCLC

ii. To determine the economic, organizational, social, ethical and legal implications of ALK tyrosine kinase inhibitors given as monotheraphy to treat patients with advanced and metastatic ALK positive NSCLC

Methods:

Part A: Systematic Review of Effectiveness, Safety & Cost-Effectiveness

Systematic literature search was conducted by the main author and an Information Specialist who searched for published articles pertaining to ALK inhibitor for advanced ALK positive NSCLC. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to September 2022, EBM Reviews - Health Technology Assessment (3rd Quarter 2022), EBM Reviews - Cochrane Database of Systematic Review (2005 to September 2022), EBM Reviews - Cochrane Central Register of Controlled Trials (September 2022), and EBM Reviews - NHS Economic Evaluation Database (3rd Quarter 2022). Parallel searches were run in PubMed, US FDA and INAHTA database. Search was limited to articles in English and in human. The last search was performed on 10th February 2022. Additional articles were identified from reviewing the references of retrieved articles.

Part B: Economic Evaluation

A state transition model (Markov cohort simulation) was developed to compare the cost-effectiveness of two treatment strategies based on the suggestion from the clinical experts. The model structure was constructed with reference to the published studies and in consultation with experts. Three health states namely progression free state (PFS), progressed disease state (PD) and dead (D) as the absorption state were included in the model. The inputs of transition probabilities were derived from the literatures. The costs used in this analysis were based on MalaysianDRG Casemix Costing, published literatures and input from Pharmaceutical Services Program, Ministry of Health. The analyses were conducted from the perspective of Ministry of Health Malaysia and projected to lifetime

horizon with one month transition cycle. Deterministic sensitivity analysis was performed as one-way sensitivity analysis to assess the model's robustness toward change in parameters.

Results

Part A: Systematic Review of Effectiveness, Safety, Cost-effectiveness

The **28** full text articles which were finally selected in this review comprised of 16 systematic review (SR), with or without meta-analysis, network meta-analysis and 12 cost-utility analysis. All SR included were published in English language between 2016 and 2022 and were conducted in the United States, Canada, Italy, China, Hong Kong and Egypt. The primary studies included in the SR were from multicountries (Japan, South Korea, Thailand, Australia, Bosnia, Brazil, Canada, Chile, China, Costa Rica, Denmark, France, Germany, Greece, Guatemala, Israel, Mexico, New Zealand, Peru, Portugal, Russia, Singapore, Spain, Switzerland, Taiwan, Turkey, Ukraine and UK). The SR included in this review comprised mainly of SR of RCTs and another two were SR of RCT and observational studies, with a range of three to 21 primary studies included in the SR. Overall in total, this review enrolled 31,614 participants with histologically confirmed advanced ALK positive NSCLC adult patients whose ECOG status was 0 to 2 (range of 697 to 5653 participants). Some of the primary studies included in the SR were also reviewed in another SR included in this review. The longest time of follow-up documented in the review was up to 42.4 months. Of the SR assessing effectiveness and safety, 12 evaluated several ALK TKIs compared to chemotherapy or crizotinib, three evaluated alectinib and one evaluated ceritinib. There was variation in the involvement of brain metastasis in the study population. There was variation in the line of treatment of ALK inhibitors used in the study population, whereby most of the SR included studies that examined ALK inhibitors as the first and second lines, with three SR evaluated its use in the first line setting. A total of 12 cost-utility analysis studies retrieved and included in this review. The CUA were conducted in China (4), Hong Kong, Canada, US (3), France, Sweden and Greek from varying perspective namely healthcare, provider, public healthcare, payer, collective payer and patient, and societal.

Effectiveness

This review showed ALK inhibitors is beneficial in improving PFS, OS, ORR, intracranial ORR and HRQoL compared to chemotherapy or crizotinib in patients with advanced ALK positive NSCLC.

Next generation ALK inhibitors including ceritinib, alectinib, lorlatinib offered greater clinical benefit with superior PFS, OS and ORR compared to crizotinib (**as the first line treatment** in patients with advanced ALK positive NSCLC).

- Alectinib 600mg showed the highest superiority (in OS), followed by lorlatinib and ceritinib, over other interventions in all advanced ALK positive NSCLC patients.

- Lorlatinib showed the highest superiority (in PFS), followed by alectinib and brigatinib, over other interventions in advanced ALK positive NSCLC patients with brain metastasis.

- Alectinib showed the highest superiority (in ORR) followed by brigatinib in the advanced ALK positive NSCLC patients (first line setting).

Next generation ALK inhibitor improved ORR compared with crizotinib in all advanced ALK positive NSCLC and in patients with BM, [RR of 1.18(95%CI 1.10 to 1.25) to RR 2.45(95% CI 1.7 to 3.54)].

Next generation ALK inhibitor including alectinib, lorlatinib, brigatinib demonstrated superiority in OS, PFS, ORR, intracranial ORR, and HRQoL compared with chemotherapy or crizotinib in patients with advanced ALK positive NSCLC in the further line of treatment.

- Alectinib showed the highest superiority (in OS) vs chemotherapy or crizotinib in advanced ALK positive NSCLC patients in the further line setting.
  ALK inhibitors improved OS compared to chemotherapy or crizotinib in these patients with HR ranging from 0.66 to 0.84.

- Lorlatinib showed the highest superiority (in PFS) followed by alectinib and brigatinib, in both all ALK positive NSCLC patients and patients with brain metastasis (BM). ALK inhibitors improved PFS compared with chemotherapy or crizotinib in these patients (HR range 0.34 to 0.45).

- Brigatinib showed the highest superiority (in ORR), followed by lorlatinib and alectinib in advanced ALK positive NSCLC patients.
  ALK inhibitor improved **ORR** compared to chemotherapy (RR from 2.43 (95%CI 2.16 to 2.75) to 4.88(95%CI 2.18 to 10.95) from all ALK positive NSCLC patients to patients with BM.

- Lorlatinib showed the highest probability for intracranial response rate (probability of 44%).
  ALK inhibitor improved **intracranial ORR** in both naïve and pre-treated ALK positive NSCLC patients (39.2% and 44.2%, respectively).

- ALK inhibitors resulted in a large increase in the **Health-Related Quality of Life** (HRQoL) measured (HR 0.52, 95% CI 0.44 to 0.60) compared to chemotherapy.

Safety

Crizotinib, ceritinib, brigatinib, alectinib and lorlatinib were registered with USFDA, indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test, and registered with Malaysia National Pharmaceutical Regulatory Agency.

ALK inhibitors appeared safe with similar overall AE rates compared with chemotherapy. Risk of grade 3 or higher AE was not significantly different between ALK inhibitors compared to chemotherapy, or between next generation ALK inhibitor and crizotinib. The most common SAE reported were dyspnoea and pneumonia. Hepatic toxicities were more common following crizotinib and ceritinib, peripheral oedema following crizotinib and alectinib, and visual disorders was only reported with crizotinib.

Cost-effectiveness

Cost-utility analysis conducted in various countries from payer and provider perspective demonstrated that the ICER varies from $13,343/QALY to $230,661/QALY comparing ceritinib versus chemotherapy or crizotinib. Comparing alectinib versus crizotinib, the ICER

ranges from $39,312/QALY to €90,232/QALY; and comparing lorlatinib versus crizotinib or chemotheraphy the ICER ranges from €46,102/QALY to $409,667/QALY.

Ceritinib offered a cost-effective option compared to crizotinib or chemotherapy in Hong Kong and Canada. Alectinib offered a cost-effective option in the US as the first line treatment in patients with advanced ALK positive NSCLC.

Organizational

For patients with metastatic non-squamous NSCLC, the NCCN panel recommends that a minimum of the following biomarkers should be tested; EGFR mutation, ALK fusion, BRAF mutation, ROS1 fusion, and PD-L1 expression level. Biomarker testing should be done at properly accredited laboratories (minimum of Clinical Laboratory Improvement Amendment, (CLIA) accreditation). The American Society of Clinical Oncology (ASCO) living guideline (2022) recommendation for patients with ALK rearrangement, a performance status (PS) of 0-2, and previously untreated NSCLC was clinicians should offer these patients with alectinib or brigatinib or lorlatinib. For these patients, if alectinib, brigatinib, or lorlatinib are not available; clinicians should offer them with ceritinib or crizotinib.

According to the National Cancer Care Network (NCCN) 2020 guideline, Alectinib is recommended as ‘preferred’ first line therapy for patients with ALK rearranged metastatic NSCLC. The NCCN panel preference stratified first line therapy with brigatinib, ceritinib or crizotinib for patients with ALK rearranged positive metastatic NSCLC. Brigatinib and ceritinib are ‘other recommended options’, while crizotinib is useful in certain circumstances. They recommended lorlatinib as a subsequent therapy option for patients who have progressed after treatment with ALK inhibitors, on either alectinib, brigatinib or ceritinib. Lorlatinib is also subsequent therapy option for patients with ALK positive NSCLC after progression on crizotinib, followed by progression on either alectinib, brigatinib or ceritinib.

The NICE single technology appraisal (2019) recommended ceritinib as an option for untreated ALK positive advanced NSCLC in adults, if the company provides it with discount agreed in the patient access scheme. NICE recommended crizotinib as an option for untreated ALK positive advanced NSCLC in adults once a patient access scheme was agreed (2017).

Social, ethical, legal

In terms of preference, most patients felt that preventing disease progression (92%), treatment response, and improved HRQoL were very important attributes for their current treatment. In considering a new treatment; a delay in disease progression of an additional one, three and five months was perceived to be meaningful by 41.4%, 57.7% and 68.3% of patients. No evidence retrieved on ethical and legal issues related to ALK inhibitor in patients with advanced ALK positive NSCLC.

Part B: Local Economic Evaluation

The base case analysis indicated that the deterministic ICER for ceritinib was MYR290,522.43 per QALY gained, while for alectinib was MYR293,308.52 per QALY gained and lorlatinib was MYR1,053,681.82 per QALY gained. All the newer generation were above the cost-effectiveness threshold of one gross domestic product (GDP) per capita per QALY gained for Malaysia.

Conclusion

Part A: Systematic Review of Effectiveness, Safety, Cost-effectiveness

Good level of evidences retrieved on ALK inhibitor to support its use in the management of patients with advanced ALK positive NSCLC.

Overall ALK inhibitors appeared beneficial in improving PFS, OS, ORR, intracranial ORR and HRQoL compared to chemotherapy or crizotinib in patients with advanced ALK positive NSCLC at first or further line of treatment setting.

Next generation ALK inhibitors including ceritinib, alectinib, lorlatinib offered greater clinical benefit with superior PFS, ORR compared to crizotinib (as the first line treatment) in patients with advanced ALK positive NSCLC).

- Alectinib 600mg showed the highest probability (in OS and ORR) in all advanced ALK positive NSCLC patients, and lorlatinib showed the highest probability (in PFS) in NSCLC patients with brain metastasis.

Next generation ALK inhibitor including alectinib, lorlatinib, brigatinib were demonstrated to be superior in OS, PFS, ORR, intracranial ORR, and HRQoL compared with chemotherapy or crizotinib in patients with advanced ALK positive NSCLC in the further line of treatment.

- Alectinib showed the highest probability (in OS) while brigatinib (ORR) in advanced ALK positive NSCLC patients in the further line setting, compared with chemotherapy or crizotinib.
- Lorlatinib showed the highest probability (in PFS) in both all ALK positive NSCLC patients and patients with BM. Lorlatinib showed the highest probability for intracranial response rate (probability of 44%).

ALK inhibitors appeared safe with acceptable safety profile. CEA conducted in various countries from payer and provider perspective demonstrated that the ICER varies. Ceritinib offered a cost-effective option compared to crizotinib or chemotherapy in Hong Kong and Canada. Alectinib offered a cost-effective option in the US as the first line treatment in patients with advanced ALK positive NSCLC. For patients with metastatic non-squamous NSCLC, a minimum of these biomarkers (EGFR mutation, ALK fusion, BRAF mutation, ROS1 fusion, and PD-L1 expression level) should be tested at properly accredited laboratories. Many international guidelines recommended ALK inhibitors to be used in the treatment of advanced patients with NSCLC.

Part B: Economic Evaluation

From the economic evaluation, ICER for the newer generation ALK TKI; ceritinib, alectinib and lorlatinib were all higher than cost-effectiveness threshold of one GDP per capita per QALY gained for Malaysia. Among these three ALK TKIs, ceritinib and alectinib were found to be more cost-effective compared to lorlatinib. The one-way sensitivity analysis indicated that the annual discounting rate, progression free state utility values and cost of the newer generation ALK TKI have shown to be the sensitive parameters for ICER and may be a key determinant before considering it in the first line treatment for patients with advanced ALK positive non-small cell lung cancer. Reduction of drugs price demonstrated significant reduction in the ICER.

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ABBREVIATION

AEs	Adverse events or adverse effects
ALK	Alkaline Lymphoma Kinase
BM	Brain metastasis
BSC	Best supportive care
CASP	Critical Appraisal Skills Programme
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CNS-PFS	Central Nervous System Progression Free Survival
CI	Confidence interval
CrI	Credible interval
CR	Complete Response
DCR	Disease Control Rate
EML4	Echinoderm microtubule associated protein like -4
FISH	Fluorescence in situ Hybridization
HC	Historical control
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IHC	Immunohistochemistry
HR	Hazard ratio
HRQoL	Health Related Quality of Life
HR	Hazard ratio
LY	Life year
MaHTAS	Malaysian Health Technology Assessment Section
MNCR	Malaysia National Cancer Registry
MOH	Ministry of Health
NCCN	National Cancer Care Network
NICE	National Institute for Health and Care Excellent
NSCLC	Non-small cell lung cancer
ORR	Overall Response Rate
OS	Overall Survival
OSR	Overall Survival Rate
PFS	Progression Free Survival
PFSR	Progression Free Survival Rate
PSA	Probabilistic sensitivity analysis
PRISMA	Preferred Reporting Format for Systematic Review & Meta Analysis
QALY	Quality adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumor
ROB	Cochrane Risk of Bias Tool
ROBIS	National Collaborating Centre for Methods and Tools
RT PCR	Real Time Polymerase Chain Reaction
SAE	Serious adverse event
SUCRA	Surface under the cumulative ranking
TKI	Tyrosine Kinase Inhibitor
US FDA	United States Food and Drug Administration
WHO	World Health Organization
WTP	Willingness to pay

1.0 BACKGROUND

Worldwide, lung cancer is the leading cause of cancer-related death. In 2020, there were 2.2 million incident cases of lung cancer (11.7%) and 1.8 million deaths (18.0%) globally. The highest lung cancer incidence (59.6%) and mortality (61.9%) were reported in Asia.[1] In Malaysia, lung cancer is the third most common cancer, accounting for 9.8% of all cancer cases.[2] In the 25-59 age group it is the second most common cancer (13.4%) and the incidence further increases in the 60-74-year-old group (17.9%).[2] Although majority of cases were detected in current or ex-smokers, increasingly patients with minimal or no smoking history were being diagnosed.[3]

Nearly 90% of lung cancer cases in Malaysia were diagnosed at an advanced stage (stage III or stage IV).[2] The 5-year observed survival rate was only 9.0% (95%CI 8.4 to 9.7).[4] A local study of lung cancer survival at a tertiary hospital reported an overall median survival of only 18 weeks for patients presented with either stage III or stage IV disease without definitive treatment. Approximately 94% of patients with advanced stage III or stage IV disease were diagnosed with non-small cell lung cancer (NSCLC).[5]

The NSCLC accounted for nearly 85% of all lung carcinoma cases with three major pathologic subtypes; adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[6] Adenocarcinoma is the most common histological subtype of lung carcinomas diagnosed within the Malaysian population.[7] Anaplastic Lymphoma Kinase (ALK) positive NSCLC represents approximately 4% to 5% of all NSCLC patients in both Caucasian and Asian populations.[8] This still represents potentially 40,000 new cases worldwide each year, given the worldwide prevalence of NSCLC.[9] Patients with ALK rearrangements have distinct clinicopathologic features such as adenocarcinoma with signet ring or acinar histology, is typically seen in those with relatively young age, with a never or light (<10 pack years) smoking history.[10] ALK positive NSCLC patients have a high risk of developing brain metastases, as observed in at least 20% of cases at the time of the initial diagnosis.[11] These patients harbour a genetic rearrangement in the ALK gene, resulting in a novel fusion oncogene *EML4-ALK* that leads to constitutive expression of intracellular signaling pathway that promote tumour growth and survival.[12]

Until recently, the standard first-line treatments for patients with NSCLC with no driver mutations [EGFR, ALK or receptor tyrosine kinase (ROS1) genomic aberrations] was platinum doublet chemotherapy, achieving modest improvement, with median progression-free survival (PFS) of five to six months, and median overall survival (OS) of 11 months (squamous histology) to 17 months (non-squamous histology).[13,14]

The management of advanced NSCLC has transformed due to improvement in the understanding of molecular drivers of carcinogenesis. The discovery of oncogenes, such as the EGFR, ALK and the others along with the development of medications specifically targeting these mutations have led to the ability to personalize therapy. The therapeutic landscape of ALK positive NSCLC has led to the introduction of three generations of ALK TKI involving different highly potent molecules.[15] For this subgroup of advanced NSCLC patients, the treatment paradigm has evolved from non-specific curative approaches, to the use of therapy targeting particular actionable genetic mutations.[16] Patients with ALK rearrangement

have been identified as subgroup of lung cancer patients to gain survival benefit from targeted therapy.[17]

International guidelines recommended testing for ALK mutation in all non-squamous NSCLC.[18] Detecting ALK gene rearrangement in newly diagnosed NSCLC is essential as the presence of this oncogene influence treatment decision. The ALK gene rearrangement can be detected in clinical samples using several techniques, primarily fluorescence in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR), immunohistochemistry (IHC), next-generation sequencing (NGS), liquid biopsy, and new potential biomarkers such as circulating tumor cells (CTCs), cell-free DNA, and exosomes are being investigated.[19]

Majority of lung cancer patients in Malaysia are diagnosed with locally advanced or metastatic disease, hence preclude curative surgical resection.[2] Several ALK-TKI were registered with National Pharmaceutical Regulatory Agency (NPRA), however they are not available in the MOH formulary. Targeted therapies were mostly hard to afford via out-of-pocket by patients without private health insurance. Most patients who cannot afford ALK TKI opt for chemotherapy. As of now, entrecnib and ensartinib are still not registered in Malaysia. Table 2 highlight their approval and availability in public hospitals.[32] In 2019, a consensus statement on Molecular Testing for Advanced NSCLC patients localized to Malaysian setting was published. According to the document, 'must-test' biomarkers which are standard-of-care for all advanced lung cancer patients with an adenocarcinoma component who are being considered for an approved targeted therapy include testing for EGFR mutation, ALK rearrangement, ROS1 rearrangement and BRAF mutation.[16] The EGFR, ALK and PD-L1 testing are being reimbursed while the others are not.[32] However, the high cost of molecular testing and systemic therapy limit the availability of treatment options for many Malaysian population.[32] Besides that, as there have been many new ALK TKI approved for ALK positive NSCLC, the review is timely to address the increasing need to provide targeted therapy with better efficacy and lower toxicity in advanced ALK positive NSCLC patients in the country. Therefore, this assessment will evaluate whether it would be effective, safe and cost-effective to use targeted therapy, ALK TKI in the management of ALK positive advanced NSCLC patients in Malaysia as requested by a Clinical Oncologist from Kuala Lumpur Hospital.

2.0 TECHNICAL FEATURES

The *ALK* gene is located on the short arm of chromosome 2 (2p23), belongs to the insulin receptor superfamily, and encodes for the ALK protein. ALK is a transmembrane tyrosine kinase receptor, which is physiologically expressed in the nervous system during embryogenesis. ALK was originally identified in anaplastic large-cell lymphoma hence the name anaplastic lymphoma kinase. Subsequently, ALK-rearrangement (ALK-R) was identified in the pathogenesis of several cancers, including inflammatory myofibroblastic tumors, diffuse large B-cell lymphoma, esophageal squamous cell and colorectal carcinomas. In 2007, ALK gene arrangement was discovered in NSCLC. There are three types of *ALK* gene mutations: rearrangement (ALK-R), amplification (ALK-A), and point mutation. Most mutations of the *ALK* gene are in the form of a translocation with another partner gene leading to a fusion oncogene. This fusion gene then becomes overly expressed in cancers. ALK rearrangements create an oncogenic ALK tyrosine kinase that activates many

downstream signaling pathways resulting in increased cell proliferation and survival. More than 19 different ALK fusion partners have been discovered in NSCLC, including EML4, KIF5B, KLC1, and TPR.[20] The most common alteration of ALK is the fusion of ALK gene with the echinoderm microtubule associated protein like -4 (EML4) gene.[21] This gene alteration was resulted from interchromosomal inversion within the short arm of chromosome 2 joining the exons 1-13 of the EML4 gene, to exons 20-29 of ALK gene.[22] NSCLC with positive ALK-EML4 gene fusion is highly sensitive to ALK inhibition by molecules designed to target tyrosine kinase. [21]

The therapeutic landscape of ALK positive NSCLC has led to the introduction of three generations of ALK TKI involving different highly potent molecules.[23] Table 1 summarises the sequence of approval for the available ALK TKI.

Crizotinib is the first generation TKI with recommended dose of 250 mg twice daily in a 28-day cycle until disease progression or no longer tolerated by the patient. It is a multi-targeted TKI, was first discovered to inhibit the c-MET pathway but has also proved to inhibit the ALK and ROS1 gene.[24] Crizotinib was the first TKI approved in 2011 by the USFDA for metastatic NSCLC patients with ALK mutation, however almost a third of the patients had developed primary or secondary resistance within one to two years.[25]

Ceritinib is a second-generation ALK TKI which is 20 times as potent as crizotinib, with a therapeutic dose of 450 mg orally once daily, and is the initial second-generation ALK TKI approved to overcome resistance to crizotinib. In 2014, ceritinib was indicated to ALK-positive patients with disease progression on or intolerance to crizotinib, subsequently indicated as first-line therapy in 2017. Ceritinib inhibits the autophosphorylation of ALK, and the molecular targets include IGF-1 R, InsR, and ROS1. Ceritinib inhibits the most common ALK mutations, such as L1196 M, G1269A, I1171T, and S1206Y, which determine resistance to crizotinib. In patients who progressed during ceritinib treatment, secondary mutations were detected such as G1202R, F1174 C/L, C1156Y, G1202del, and L1196M. The F1174L mutation can be resistant to ceritinib but sensitive to alectinib.[26]

Alectinib is a highly potent second-generation ALK that also has RET (Rearranged during Transfection) gene activity inhibitor, with recommended twice-daily dose of 600 mg.[27] Alectinib is indicated for NSCLC patients with ALK rearrangement who have benefited previously from crizotinib, approved in 2015 and subsequently indicated as first-line therapy in 2017. Due to its chemical structure, it is efficient for patients with crizotinib-resistant ALK mutations.[28]

Brigatinib is a highly potent selective second generation ALK inhibitor. It was approved by USFDA as a first line option for patients with ALK positive NSCLC in 2020, with recommended dose of 90mg orally once daily for first seven days then increase to 180mg orally once daily, until disease progression or unacceptable toxicity.[29]

In order to overtake acquired resistance, prolong the control of the disease, and manage CNS disease, several highly potent next-generation ALK TKIs have been developed such as lorlatinib and ensartinib.[30] Lorlatinib is a third-generation ALK- and ROS1-inhibitor, a selective, brain penetrating ALK TKI, designed to target mutations which drive resistance to crizotinib and next-generation TKIs. Recommended dose is 100 mg once daily, approved in 2018 by the USFDA as the first-line therapy for metastatic NSCLC patients and ALK

rearrangement with progressive disease on crizotinib and other ALK inhibitors.[31] Lorlatinib is a macrocyclic TKI, smaller and more compact compared to the first and second generation which is an acyclic TKI. [24]

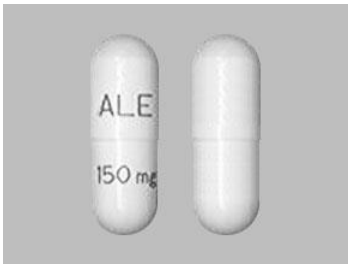
Ensartinib is a novel second-generation ALK inhibitor created to improve the activity on CNS metastases. This small molecule displayed activity against MET, Axl, ABL, EPHA2, LTK, ROS1, and SLK genes. Entrectinib is a potent, selective, oral inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK, with the ability to cross the blood - brain barrier and possess a strong intracranial activity.[24]

Table 1: ALK TKI for treatment of NSCLC approval status

Drugs	FDA Indication	Date of USFDA Approval	MOH Registration Status	MOH Drugs Formulary
Crizotinib	• Patients with late-stage (locally advanced or metastatic), NSCLC who express the abnormal ALK gene • Patients with metastatic NSCLC whose tumors are ALK or ROS1-positive as detected by an FDA-approved test.	2011 11 March 2016	Yes Xalkori 200mg & 250mg Capsules (Pfizer)	Not available (NA)
Ceritinib	• For the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test	26 May 2017	Yes Zykadia 150mg Hard Capsules (Novartis)	NA
Alectinib	• For the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.	6 November 2017	Yes Alecensa Hard Capsules 150mg (Roche)	NA
Brigatinib	• For the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.	22 May 2020	Yes Alunbrig (Brigatinib) 30mg, 90mg & 180mg Film-Coated Tablet (TakedaPharmaceutical)	NA
Lorlatinib	• For the treatment of adult patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.	3 March 2021	Yes Lorviqua 25 mg & 100 Film-Coated Tablets (Pfizer)	NA
Entrectinib	• Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive. • Adult and pediatric patients 12 years of age and older with solid tumors that: ○ have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, ○ are metastatic or where surgical resection is likely to result in severe morbidity, and ○ have progressed following treatment or have no satisfactory alternative therapy.	15 August 2019	NA	NA

a) Crizotinib (xalkori)

b) Ceritinib (zykadia)



c) Alectinib (alecensa)

d) Lorlatinib (lorbrena)

Figure 1: Physical appearance of several ALK TKI inhibitors

3.0 POLICY QUESTION

Should targeted therapy (ALK tyrosine kinase inhibitor) be used as a standard treatment option for patients with advanced and metastatic ALK positive NSCLC in the Ministry of Health hospitals?

4.0 OBJECTIVE

4.1 The following are the objectives of this review:

iii. To assess the comparative effectiveness and safety of ALK tyrosine kinase inhibitors given as monotheraphy to treat patients with advanced and metastatic ALK positive NSCLC

iv. To determine the economic, organizational, social, ethical and legal implications of ALK tyrosine kinase inhibitors given as monotherapy to treat patients with advanced and metastatic ALK positive NSCLC

5.0 PART A: SYSTEMATIC REVIEW OF LITERATURE

5.1 METHODS

5.1.1 Literature search strategy

Systematic literature search was developed by the main author and *Information Specialist* who searched for published articles pertaining to ALK inhibitor for advanced ALK positive NSCLC. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions® 1946 to September 2022, EBM Reviews - Health Technology Assessment (3rd Quarter 2022), EBM Reviews - Cochrane Database of Systematic Review (2005 to September 2022), EBM Reviews - Cochrane Central Register of Controlled Trials (September 2022), and EBM Reviews - NHS Economic Evaluation Database (3rd Quarter 2022). Parallel searches were run in PubMed, US FDA and INAHTA database. Search was limited to articles in English and in human. Detailed search strategy is as in **Appendix 3**. The last search was performed on 15 September 2022. Additional articles were identified from reviewing the references of retrieved articles.

5.1.2 Study selection

Two dedicated reviewers (RS and BAG) independently screened the titles and abstracts against the inclusion and exclusion criteria as shown below and evaluated the selected full-text articles for final article selection. Disagreement was resolved by discussion.

Inclusion criteria:

a.	**Population**	Patients with advanced (stage III or IV) NSCLC harbouring ALK gene rearrangement
b.	**Intervention**	ALK Tyrosine Kinase Inhibitors, ALK inhibitors (Included crizotinib, ceritinib, alectinib, lorlatinib)
c.	**Comparator**	• Chemotherapy • First generation ALK TKI (crizotinib)

d.	**Outcomes**	i. Effectiveness Overall survival (OS) Progression free survival (PFS) Overall response rate (ORR) Health-related quality of life (HRQoL) ii. Safety Adverse events, Complications iii. Economic impact Cost-effectiveness Cost-utility analysis Cost-benefit analysis Cost analysis Any other measure of economic outcome iv. Organizational, social, ethical and legal implications
e.	**Study design**	HTA reports, systematic review with or without meta-analysis, economic evaluation studies
f.	Full text articles published in English	

Exclusion criteria:

a.	**Study design**	Animal study, laboratory study, case report, case series, narrative review
b.	Non-English full text articles	
c.	Studies evaluating ALK inhibition with other systemic treatment	

5.1.3 Critical appraisal of literature/ assessment of risk of bias

The risk of bias or quality assessment (methodology quality) of all retrieved literatures was assessed depending on the type of the study design; using the relevant checklist of National Collaborating Centre for Methods and Tools (ROBIS) for Systematic Review and Meta-analysis, and Critical Appraisal Skill Programme (CASP) for economic studies. All full text articles were graded based on guidelines from the *U.S. / Canadian Preventive Services Task Force* (**Appendix 1**).

5.1.4 Analysis and synthesis of evidence

Data extraction strategy

Data were extracted from included studies by a reviewer using a pre-designed data extraction form (*Evidence Table* as shown in **Appendix 4**) and checked by another reviewer. Disagreements were resolved by discussion and the extracted data was also presented and discussed with the *Expert Committee*. The data extracted was as follows:

i. Details of method and study population characteristics
ii. Detail of intervention and comparators
iii. Details of individual outcomes specified

Methods of data synthesis

Data on the accuracy, effectiveness, safety and cost-effectiveness associated with ALK TKI for NSCLC were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

5.2 RESULTS

5.2.1 Selection of included articles

An overview of the systematic search and selection of the studies are illustrated in **Figure 2.** A total of **223** records were identified through the Ovid interface and PubMed while **14** were identified from other sources (references of retrieved articles). Following the removal of **two** duplicates, **235** titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, **35** relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria to the **35** full text articles, **28** full text articles were included. **Seven** articles were excluded following irrelevant study design (n=1), irrelevant population (1), irrelevant intervention (n=4) and irrelevant outcome (1). The excluded articles were listed as in **Appendix 5**.

The **28** full text articles which were finally selected in this review comprised of 16 systematic review (with or without meta-analysis, network meta-analysis) and 12 economic evaluation studies.

All SR included were published in English language between 2016 and 2022 and were conducted in the United States, Canada, Italy, China, Hong Kong and Egypt. The primary studies included in the SR were from multicountries (Japan, South Korea, Thailand, Australia, Bosnia, Brazil, Canada, Chile, China, Costa Rica, Denmark, France, Germany, Greece, Guatemala, Israel, Mexico, New Zealand, Peru, Portugal, Russia, Singapore, Spain, Switzerland, Taiwan, Turkey, Ukraine and UK). The SR included in this review comprised mainly of SR of RCTs and another two were SR of RCT and observational studies, with a range of three to 21 primary studies included in the SR. Overall in total, this review enrolled 31,614 participants with histologically confirmed advanced ALK positive NSCLC adult patients whose ECOG status was 0 to

2 (range of 697 to 5653 participants). Some of the primary studies included in the SR were also reviewed in another SR included in this review. The longest time of follow-up documented in the review was up to 42.4 months. Of the SR assessing effectiveness and safety, 12 evaluated several ALK TKIs compared to chemotherapy or crizotinib, three evaluated alectinib and one evaluated ceritinib. There was variation in the involvement of brain metastasis in the study population. There was variation in the line of treatment of ALK inhibitors used in the study population, whereby most of the SR included studies that examined ALK inhibitors as the first and second lines, with three SR evaluated its use in the first line setting. The SR was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist guideline.

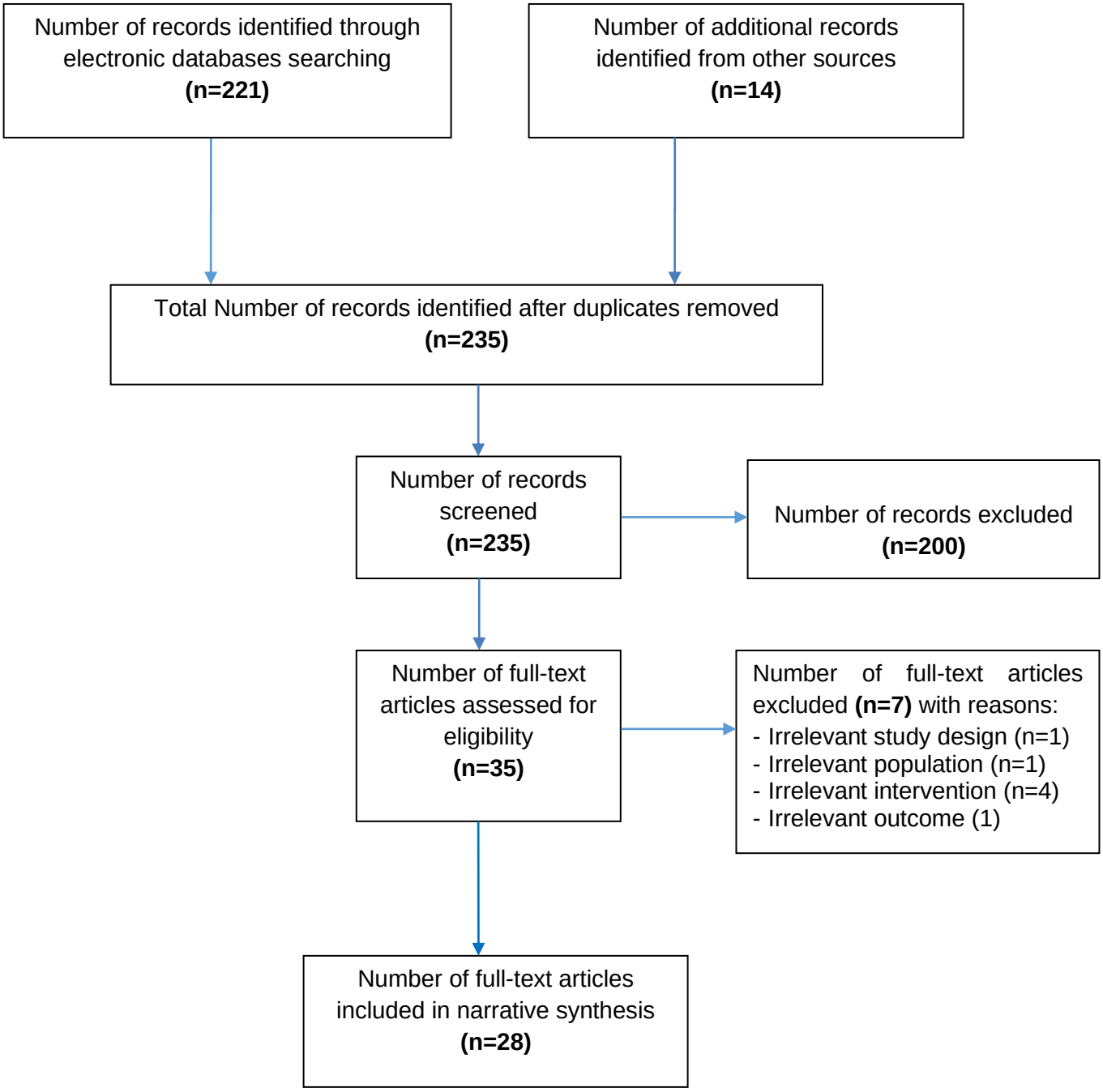


Figure 2: Flow chart of article retrieval and study selection

5.2.2 Quality assessment/ risk of bias

Risk of bias was assessed using Risk of Bias in Systematic Reviews (ROBIS) for systematic review and meta-analysis, and Critical Appraisal Skill Programme (CASP) checklist for observational and economic studies. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias. The risk of bias of the included studies was assessed independently by two reviewers. Any disagreements were resolved through discussion until consensus was reached.

Risk of bias assessment for included systematic review and meta-analysis

Sixteen SR were included in this review. The risk of bias of each of the included study is displayed as both Table 2 and Figure 3 below. Two SR included in the safety section were having overall high risk of bias. Otherwise, the rest of the SR were having low risk of bias.

Table 2: Summary of risk of bias assessment for systematic review using ROBIS

Articles	**Domain: Study eligibility criteria**	**Domain: Identification & Selection of studies**	**Domain: Data collection & Study appraisal**	**Domain: Synthesis & Findings**	**Overall risk of bias**
Effectiveness & Safety (11)					
Cameron et al 2022	+	+	+	+	+
Breadner et al 2020	+	+	+	+	+
Zhao et al 2021	+	+	+	+	+
Ma H et al 2021	+	+	+	+	+
Wang L et al 2021	+	+	+	?	+
Elliott J et al 2020	+	+	+	+	+
Zeng Q et al 2022	+	?	+	+	+
Tang H et al 2021	+	+	+	+	+
Yang Y et al 2020	+	+	+	+	+

Zhao X et al 2018	+	+	+	+	+
Petrelli F et al 2018	+	+	+	+	+
Safety (5)					
Cirrne et al 2021	+	+	+	+	+
Costa et al 2018	+	+	-	?	?
Li J et al 2019	+	+	+	+	+
Kassem L et al 2019	+	+	-	-	-
Pellegrino et al 2018	?	+	-	-	-

Risk of bias assessment for included economic evaluation

Twelve cost-effectiveness analyses were included in this assessment and risk of bias of individual CEA were summarised in Figure 3. Overall, the included studies were good, with low risk of bias. Only three studies were found with unclear criteria on the description of competing alternatives. There was low risk of bias for the rest of the criteria's in all the included studies.

Figure 3: Summary of risk of bias assessment for economic evaluation using CASP checklist

5.2.3 Effectiveness

There were 11 SR retrieved on the effectiveness of ALK TKI in the treatment of patients with advanced ALK positive NSCLC.

5.2.3.1 First Line Setting (Exclusively / Partly)

- **Overall Survival**

Summary of effectiveness of ALK inhibitor of the main outcomes; OS, PFS and ORR were summarised in the respective table below.

Table 2: Summary of Overall Survival outcome for ALK inhibitors in the first line treatment setting

Intervention vs Comparator	SR (n)	Effect estimate
Next generation(C,Cr,A,L,E) vs chemotherapy or crizotinib	Ma H et al 2021 9 RCT (2484)	No difference**(among ALK inhibitor or between ALK inhibitor & chemotherapy **Bayesian ranking** ***Alectinib 35.9%*** *Lorlatinib 30.6%* *Ensartinib 11.8%*
Next generation (A, L,B) vs crizotinib	Wang L et al 2021 5 RCT (1111)	**No difference****
Next generation vs crizotinib	Cameron et al 2022 6 RCT (1611)	**HR 0.71 (95% CI 0.56 – 0.90)**

*C:Ceritinib, Cr:Crizotinib, A:Alectinib, L:Lorlatinib, E:Ensartinib; **:No details available*

- **Progression Free Survival**

Table 3: Summary of Progression Free Survival (PFS) outcome for ALK inhibitors in the first line treatment setting

Intervention vs Comparator	SR (n)	Effect estimate
Next generation (C,C,A,L,E) vs chemotherapy or crizotinib	Ma H et al 2021 9 RCT (2484)	**HR 0.22 (95%CrI 0.50 – 0.89) Lorlatinib vs Ceritinib** **HR 0.28 (95%CrI 0.11 – 0.69) Lorlatinib vs Crizotinib** **HR 0.12 (95%CrI 0.04 – 0.36) Lorlatinib vs Chemo** HR 0.32 (95%CrI 0.09 -1.10) Alectinib vs Ceritinib **HR 0.41 (95%CrI 0.21 – 0.77) Alectinib vs Crizotinib** **HR 0.18 (95%CrI 0.07 – 0.42) Alectinib vs Chemo** **Bayesian ranking** ***Lorlatinib 63.7%*** *Alectinib 300mg 17.6%* *Alectinib 600mg 7.2%*
Next generation (A, L,B) vs crizotinib	Wang Let al 2021 5 RCT (1111)	**HR 0.54 (95% CI 0.31 – 0.94) Lorlatinib vs Brigatinib** **HR 0.59 (95% CI 0.37 – 0.94) Lorlatinib vs Crizotinib** **Bayesian ranking** ***Lorlatinib (97.5%) (all part)*** ***Lorlatinib (63.3%) (patient with CNS)***
Next generation vs crizotinib	Cameron et al 2022 6 RCT (1611)	**HR 0.39(95% CI 0.33 – 0.46) – All participants** **HR 0.25(95% CI 0.19 – 0.34) – Patient with CNS**

C:Ceritinib, Cr:Crizotinib, A:Alectinib, L:Lorlatinib, E:Ensartinib

- **Overall Response Rate (ORR)**

Table 4: Summary of Overall Response Rate (ORR) outcome for ALK inhibitors in the first line treatment setting

Intervention vs comparator	SR (n)	Effect estimate
Next generation (C,C,A,L,E) vs chemotherapy or crizotinib	Ma H et al 2021 9 RCT (2484)	**Bayesian ranking** ***Alectinib 300mg (63.9%)*** *Brigatinib (15.1%)*
Next generation (A, L, B) vs crizotinib	Wang L et al 2021 5 RCT (1111)	**Bayesian ranking** ***Lorlatinib (48%) (Highest)***
Next generation vs crizotinib	Cameron et al 2022 5 RCT (1229) 4 RCT (18)	**RR 1.18(95% CI 1.10 – 1.25) - All participants** **RR 2.45(95% CI 1.7 – 3.54) - Patient with BM**

C:Ceritinib, Cr:Crizotinib, A:Alectinib, L:Lorlatinib, E:Ensartinib

a) First line setting (previously untreated)

Next generation ALK TKI versus crizotinib

Cameron LB et al. (2022) in a SR evaluated the safety and efficacy of ALK inhibitors given as monotherapy to treat advanced ALK-rearranged NSCLC. In the review, systematic search was conducted from Cochrane Lung Cancer Group Specialised Register, Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE from 2007 until 7 January 2021. The review included 11 RCTs (2874 participants) comparing ALK inhibitors with cytotoxic chemotherapy or another ALK inhibitor in

individuals with incurable locally advanced or metastatic pathologically confirmed ALK-rearranged NSCLC. Of the 11 RCTs, six studies compared an ALK inhibitor (crizotinib, ceritinib and alectinib) to chemotherapy, while five studies compared a next-generation ALK inhibitor (**alectinib, brigatinib, and lorlatinib**) to crizotinib.

Progression-free survival (PFS) was defined as the time from date of randomisation to date of objective disease progression by Response Evaluation Criteria in Solid Tumours (RECIST 1.1) or death from any cause, whichever occurred first. Adverse event (AE) grade (1 to 5) was defined by common terminology criteria for AEs (CTCAE v4). Overall survival (OS) was defined as time from date of randomisation to date of death from any cause, or study end date if the participant was alive. Overall response rate (ORR) was measured by RECIST 1.1 criteria, and health-related quality of life (HRQoL) evaluated based on validated generic or disease-specific scale.

Three studies recruited treatment-naïve participants (ALESIA 2019, ALEX 2017 and CROWN 2020), and two studies recruited participants who were permitted to have had one line of previous chemotherapy (ALTA-1L 2019 and J-ALEX 2017).

- **Progression Free Survival (PFS)**

All participants

Next-generation ALK inhibitors resulted in a large increase in PFS (all participants) compared with crizotinib (HR 0.39, 95% CI 0.33 to 0.46),(five RCTs, 1263 participants, high-certainty evidence). (Figure 4)

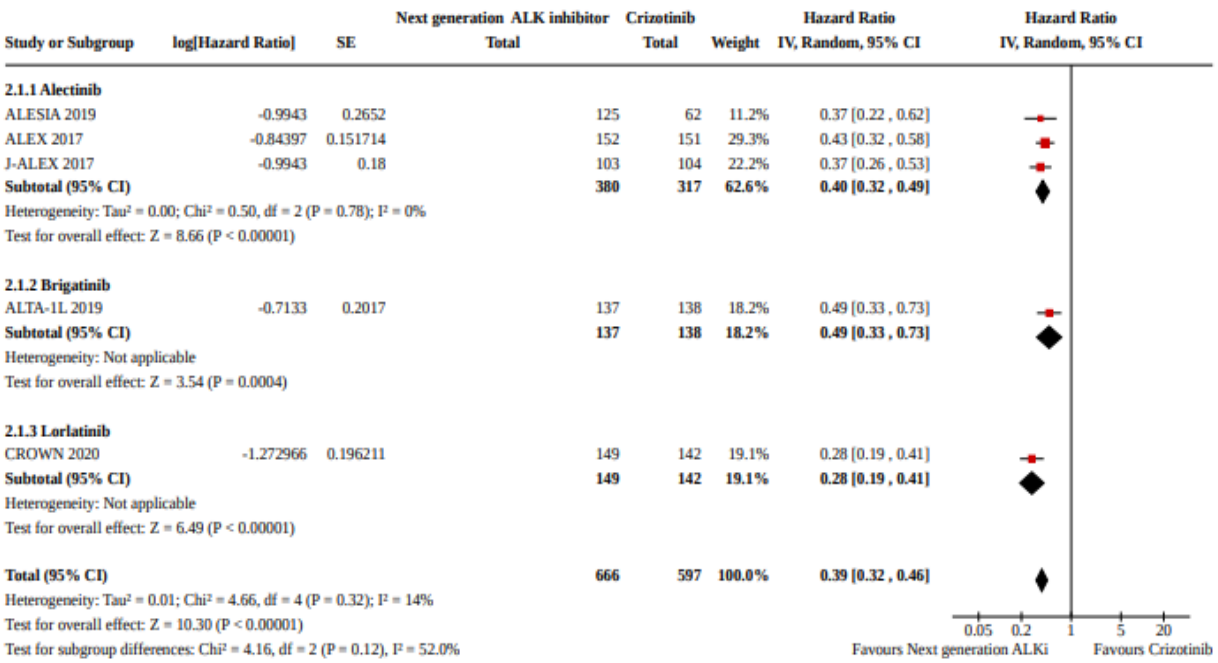


Figure 4: Next generation ALK TKI versus crizotinib, progression free survival
Source: Cameron LB et al. (2022)

Patients with CNS disease

Next generation ALK inhibitors improved PFS in people with CNS disease (baseline brain metastasis) compared with crizotinib (HR 0.25, 95%CI 0.19 to 0.34), (five RCTs, 406 participants).

- **Overall Survival (OS)**

Next-generation ALK inhibitors likely increase OS compared to crizotinib (HR 0.71, 95% CI 0.56 to 0.90), (five RCTs, 1263 participants, moderate-certainty evidence).(Figure 5)

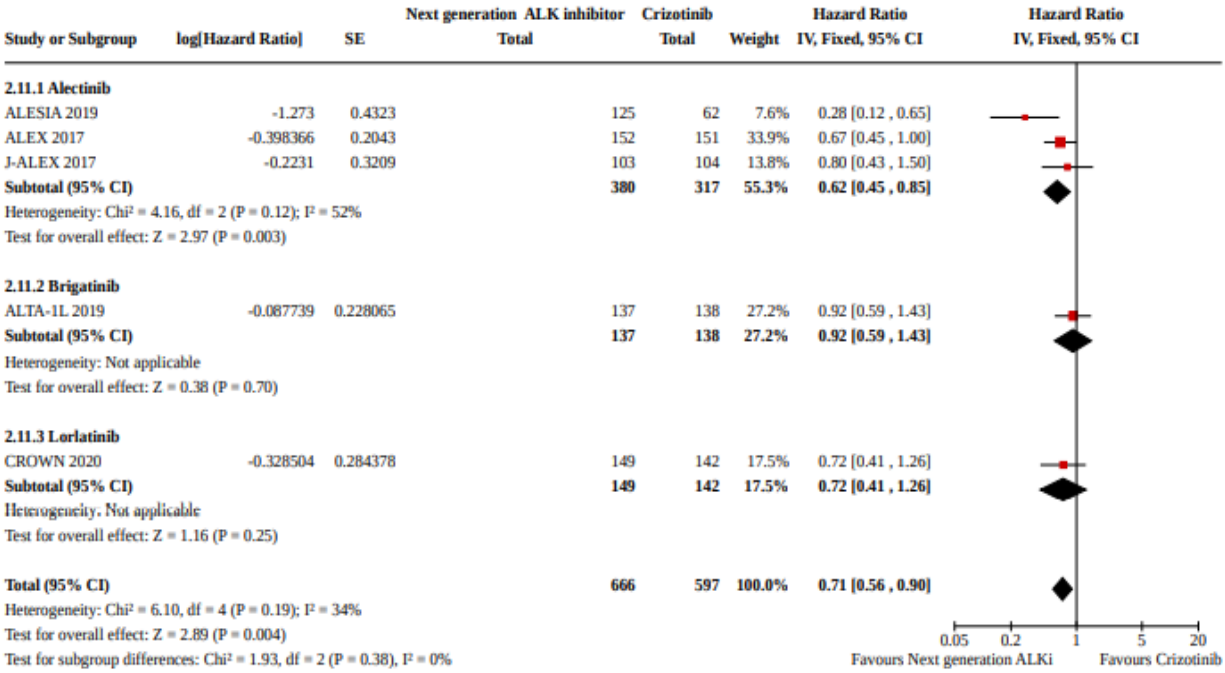


Figure 5: Next generation ALK TKI versus crizotinib, progression free survival
Source: Cameron LB et al. (2022)

- **Overall Response Rate (ORR)**

All participants

Next-generation ALK inhibitors slightly increased ORR compared to crizotinib, (RR 1.18, 95%CI 1.10 to 1.25), (five RCTs, 1229 participants).

Patients with CNS disease

Next-generation ALK inhibitors increased ORR in patients with measurable brain metastases (RR 2.45, 95%CI 1.7 to 3.54), (four RCTs, 138 participants).

- **Adverse Event**

Overall AE

Next-generation ALK inhibitors resulted in no difference in overall AE compared to crizotinib.(RR 1.00, 95% CI 0.98 to 1.01)(five RCTs, 1263 participants, moderate certainty evidence).

Grade 5 AE

Next-generation ALK inhibitors resulted in no difference in grade five AE compared to crizotinib.(RR 0.85, 95% CI 0.49 to 1.47)(five RCTs, 1263 participants, low certainty evidence).

Next generation ALK inhibitors, including alectinib, brigatinib and lorlatinib achieve superior PFS and OS compared to crizotinib as the first line treatment for patients with advanced ALK rearranged NSCLC. Next-generation ALK inhibitors including alectinib, brigatinib, and lorlatinib are the preferred first systemic treatment for these patients. Next-generation inhibitors have not been compared to each other, and it is unknown which should be used first and what subsequent treatment sequence is optimal. [17 level I]

Next generation ALK TKI (alectinib, brigatinib, ensartinib, lorlatinib) vs chemotheraphy or crizotinib

Ma H et al. (2021) in a network meta-analysis (NMA) aimed to compare the efficacy and safety of first line systemic therapeutic options used for the treatment of ALK rearranged NSCLC. The NMA included nine RCTs (2484 patients) from trials published between 2014 to 2021. Of the nine RCTs, three compared ALK TKI vs chemotherapy: [crizotinib (2), ceritinib (1)], while six compared next generation ALK TKI vs crizotinib [Alectinib (3), Brigatinib (1), Ensartinib (1), Lorlatinib (1)]. Systematic search was done from the PubMed, Embase, Cochrane Library, and ClinicalTrials.gov databases up to 10 September 2021. Search was also done from several relevant international conferences (American Society of Clinical Oncology, European Society of Medical Oncology, World Cancer Conference from 2016-2021.The NMA included phase II or III RCTs involving adult patients with histologically or cytologically confirmed advanced (stage III/IV/ recurrent) NSCLC with ALK- rearrangement, comparing any two or more first line treatments. Current standard of first-line therapy for patients with advanced ALK-rearranged NSCLC is treatment with ALK-TKIs, the comparator of this meta-analysis is dominated by ALK-TKI. Risk of bias of the included studies was assessed using a modified version of the Cochrane Collaboration's Risk-of Bias Tool. The NMA followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) extension statement for NMA. The prespecified outcomes were progression free survival (PFS), overall survival (OS), objective response rate (ORR), and adverse events of grade 3 or higher (Grade ≥ 3 AEs). The PFS and OS were analysed as a survival outcome and reported as Hazard Rate (HR) with an associated 95%CrI. Objective Response Rate (ORR) and Grade ≥ 3 AEs were analysed as a binary outcome and reported as odds ratio (OR) with an associated 95%CrI. The NMA were performed with a Bayesian hierarchical random effects model using GeMTC (version 0.14.3) and R (version 3.5.3; Package gemtc).

- **Progression Free Survival (PFS)**

The NMA by Ma H et al. (2021) found lorlatinib and alectinib (300mg and 600mg) were significantly superior to ceritinib, crizotinib and chemotherapy.

Lorlatinib yielded superior PFS against ceritinib (HR 0.22, 95%CrI 0.05 to 0.89), crizotinib (HR 0.28, 95%CrI 0.11 to 0.69) and against chemotherapy (HR 0.12, 95%CrI 0.04 to 0.36).

Alectinib 600mg similarly showed better PFS against ceritinib (HR 0.32, 95%CrI 0.09 to 1.10), crizotinib (HR 0.41, 95%CrI 0.21 to 0.77) and against chemotherapy (HR 0.18, 95%CrI 0.07 to 0.42), this result is broadly consistent with the results with alectinib 300 mg. According to the Bayesian ranking profiles, the highest probability for better PFS was lorlatinib (63.7%), followed by alectinib 300mg (17.6%), alectinib 600mg (7.2%).

- *PFS: Subgroup - Patients with CNS metastasis*

In patients with baseline CNS metastases, according to the Bayesian ranking profiles, the highest probability for better PFS was alectinib 300 mg (63.9%) followed by brigatinib (15.1%).

- *PFS: Subgroup - Patients without CNS metastasis*

For the patients without baseline CNS metastases, lorlatinib was the most preferred treatment option. According to the Bayesian ranking profiles, the highest probability for better PFS was lorlatinib (91%) followed by alectinib 300 mg (2.7%)

- **Overall Survival (OS)**

They found no significant OS difference among the ALK-TKIs, or between the ALK-TKIs and chemotherapy. However, alectinib 600 mg was a preferred option for OS. According to the Bayesian ranking profiles, the highest probability for better OS was alectinib 600mg (35.9%) followed by lorlatinib (30.6%) and ensartinib (11.8%).

- **Objective Response Rate (ORR)**

They found no significant difference for ORR among the ALK TKIs. According to the Bayesian ranking profiles, the highest probability for better ORR was alectinib 300 mg (37%) followed by lorlatinib (21%) and alectinib 600 mg (13%).

- **Adverse Events (AE)**

The study found the most likely intervention to be associated with AE (cause of Grade ≥ 3 AEs) was ceritinib (60%) followed by lorlatinib (18%), according to the Bayesian ranking profiles.

The author's concluded that alectinib (300 mg and 600 mg) and lorlatinib had favourable effectiveness with tolerable adverse effects in the first-line treatment for major population of advanced NSCLC patients with ALK-rearrangement. However, since there is little comparative evidence on the treatment options, there should be more head-to-head RCTs between the second and third-generation ALK-TKIs to fully determine the best treatment options. Furthermore, it is necessary to carry out reasonable sequential treatment following ALK-TKI drug resistance. [33] level I

<u>Next generation ALK TKI (alectinib, brigatinib, lorlatinib) vs crizotinib</u>

Wang L et al. (2021) conducted another NMA to help inform treatment choice between alectinib, brigatinib and lorlatinib in ALK inhibitor naïve/untreated advanced ALK positive NSCLC patients. This NMA involved five RCTs (1111 subjects), comprised of

alectinib vs crizotinib (three trials), brigatinib vs crizotinib (one trial) and lorlatinib vs crizotinib (one trial). They included only studies with ALK inhibitor-naive or previously untreated (ALK inhibitor-naive and chemotherapy-naive) advanced NSCLC. Studies that provided sufficient information to allow the calculation of crude Hazard Ratios (HRs) for PFS, OS, response rates, AE were included. Systematic search was conducted up to January 2021 for relevant articles. Primary outcome was PFS, while secondary outcomes were OS, response rate, and AE. Risk of bias was assessed using the methodology described in the Cochrane Collaboration Handbook. Network meta-analyses were performed in the Bayesian framework. For ranking probabilities evaluation, they used the surface under the cumulative ranking (SUCRA) curve which provides a numerical summary of the rank distribution of each treatment on PFS, OS, response rate and adverse reaction. The larger the SUCRA curve value (up to 1), the higher the probability of being the first ranked intervention. Network meta-analyses were performed using OpenBUGS version 3.2.3.

- **Progression Free Survival**

Untreated (ALK inhibitor naïve and chemotherapy naïve)

They found lorlatinib had better PFS than brigatinib (**HR 0.54, 95%CrI 0.31 to 0.94**) and better compared to alectinib (**HR 0.59, 95% CrI 0.37 to 0.94)** in untreated patients (both ALK inhibitor and chemotherapy naïve).(Figure 6)

ALK inhibitor naïve

The study found lorlatinib significantly improved PFS compared to brigatinib (**HR 0.57, 95%CrI 0.34 to 0.95**), and compared to alectinib (HR 0.65, 95%CrI 0.42 to 1.01) in ALK inhibitor naïve patients. (Figure 6)

Based on ranking, lorlatinib had the highest probability for the best PFS in both groups (as in figure 4):-

- Untreated patients **(both ALK inhibitor and chemotherapy naïve)**(probability of 97.5%),
- ALK inhibitor naïve patients (probability of 96.4%)

Subgroup analysis (CNS metastasis population)

In patients with CNS metastasis, lorlatinib had the highest probability for the best PFS (probability of 63.3%), among lorlatinib, alectinib, brigatinib and crizotinib.

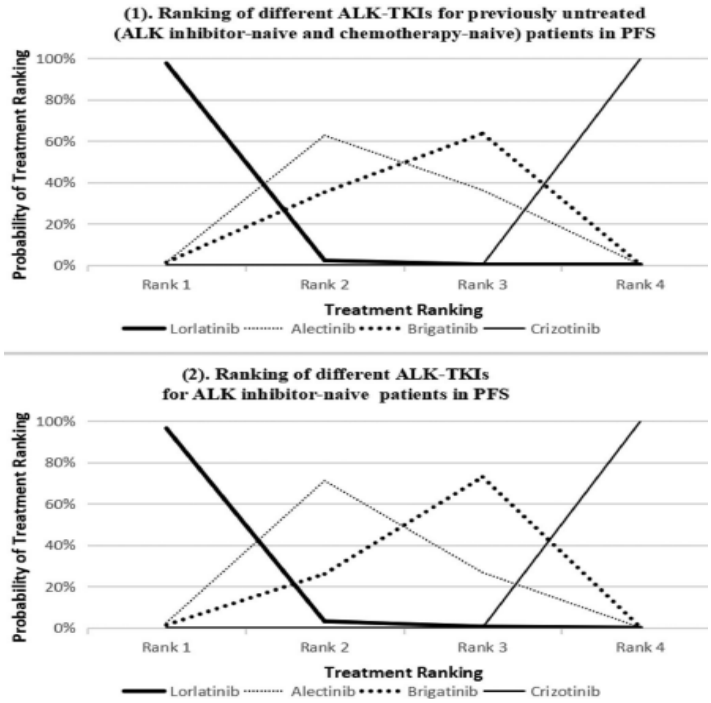


Figure 6: Treatment ranking for different ALK inhibitor in PFS. Source: Wang L et al. (2021)

- **Overall Response Rates (ORR)**

They found lorlatinib had the highest probability to reach the best overall confirmed response rates (probability of 48%).

- **Intracranial Response Rates (Intracranial RR)**

Similarly, lorlatinib had the highest probability to reach the best Intracranial confirmed response rates (probability of 44%). (Figure 7).[34 level I]

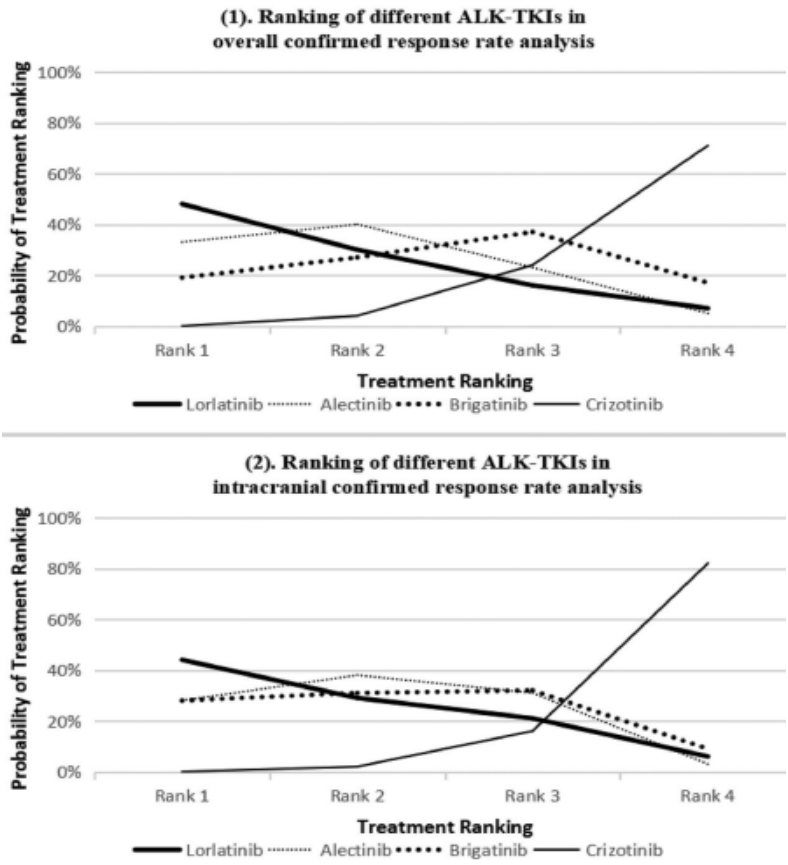


Figure 7: Treatment ranking for different ALK inhibitor in ORR, intracranial RR
Source: Wang L et al. (2021)

5.2.3.2 Regardless of line of treatment (further line)

- **Overall Survival (OS)**

Summary of the effectiveness of main outcomes, PFS, OS and ORR of ALK inhibitor in the further line setting were as summarised below.

Table 5: Summary of Overall Survival outcome for ALK inhibitors in further line of treatment for ALK positive NSCLC patients

Intervention vs Comparator	SR (n)	Effect estimate for OS
ALK inhibitor vs chemotherapy	Cameron et al 2022 6 RCT (1611)	**HR 0.84 (95% CI 0.72 to 0.97)**
Next generation ALK vs crizotinib or chemotherapy	Breadner et al 2020 10 RCT (2583)	**HR 0.84 (95% CI 0.72 to 0.97)(vs chemotherapy)** HR 0.66 (95% CI 0.43 to 1.02)(vs crizotinib)
Next generation ALK vs chemotherapy or crizotinib	Zhao B et al 2021 11 RCT (2687 + 991)	**Ranking of individual treatment** ***Alectinib 0.846*** *Lorlatinib 0.669* *Ceritinib 0.479* *Brigatinib 0.442* *Crizotinib 0.365* *Chemo 0.20*

		HR 0.29 (95% CrI 0.03 to 1.68) - alectinib HR 0.41 (95% CrI 0.04 to 4.13) - lorlatinib HR 0.63 (95% CrI 0.10 to 4.25) - ceritinib
Alectinib vs crizotinib	Zeng Q et al 2022 7 RCT (697)	**HR 0.66 (95%CI 0.47 to 0.92)**

- **Progression Free Survival**

Table 6: Summary of PFS outcome for ALK inhibitors in further line of treatment in ALK positive NSCLC patients

Intervention vs Comparator	SR (n)	Effect estimate
ALK inhibitor vs chemotherapy	Cameron et al 2022 6 RCT (1611)	**HR 0.45 (95% CI 0.40 to 0.52)**
Next generation ALKi vs chemotherapy or crizotinib	Breadner et al 2020 10 RCT (2583)	**HR 0.44 (95% CI 0.35 to 0.54) (vs chemotherapy)** **HR 0.38 (95% CI 0.29 to 0.51) (vs crizotinib)**
Next generation ALKi vs chemotherapy or crizotinib	Zhao B et al 2021 11 RCT (2687)	**Ranking of ind treatment (all patients)** ***Lorlatinib 0.976*** *Alectinib 0.795* *Brigatinib 0.722* **Ranking of ind treatment (patients with BM)** ***Lorlatinib 0.973*** *Alectinib 0.775* *Brigatinib 0.72* **HR 0.01 (95% CrI 0.001 to 0.12) - lorlatinib** **HR 0.05 (95% Cr 0.01 to 0.21) - alectinib** **HR 0.07 (95% Cr 0.007 to 0.76) - brigatinib**
Alectinib vs Crizotinib	Tang H et al 2021 3 RCT (697)	**HR 0.34 (95% CrI 0.21 to 0.55)**
Alectinib vs Crizotinib	Zeng Q et al 2022 7 RCT (697)	**HR 0.35 (95% CrI 0.25 to 0.49)**
Alectinib vs Crizotinib	Yang Y 2020 10 Studies (2377)	**HR 0.41 (95% CrI 0.29 to 0.53)**

- **Overall Response Rate (ORR)**

Table 7: Summary of ORR for ALK inhibitors in further line of treatment ALK positive NSCLC patients

Intervention vs Comparator	SR (n)	Effect estimate for ORR
ALK inhibitor vs Chemotherapy	Cameron et al 2022 6 RCT (1611)	**RR 2.43 (95% CI 2.16 to 2.75) (all participant)** **RR 4.88 (95% CI 2.18 to 10.95) (patient with Brain Metastasis)**
Next generation ALK inhibitor vs crizotinib or chemotherapy	Breadner et al 2020 10 RCT (2583)	**RR 2.74 (95% CI 1.90 to 3.95) - vs chemotherapy** **RR 2.16 (95% CI 1.08 to 1.24) - vs crizotinib)**
Alectinib vs Crizotinib	Zhao B et al 2021 11 RCT (2687)	Ranking of individual treatment (SUCRA Value) **Brigatinib 0.824** Lorlatinib 0.792 Alectinib 0.699
Alectinib vs Crizotinib	Tang H et al 2021 3 RCT (697)	**OR 2.07 (1.41 - 3.06)**
Alectinib vs Crizotinib	Zeng Q et al 2022 7 RCT (697)	**RR 0.87 (95% CI 0.80 – 0.94)**

ALK inhibitor versus chemotherapy

Cameron LB et al. (2022) in the SR evaluated the safety and efficacy of ALK inhibitors given as monotherapy to treat advanced ALK-rearranged NSCLC. The review included 11 RCTs (2874 participants) comparing ALK inhibitors with cytotoxic chemotherapy or another ALK inhibitor in individuals with incurable locally advanced or metastatic pathologically confirmed ALK-rearranged NSCLC. Of the 11 RCTs, six studies compared an ALK inhibitor (crizotinib, ceritinib and alectinib) to chemotherapy, while five studies compared a next-generation ALK inhibitor (alectinib, brigatinib, and lorlatinib) to crizotinib.

These were the pool results for ALK inhibitor compared to chemotherapy from Cameron LB et al. (2021).

- **Progression Free Survival**

All participants
They found ALK inhibitors resulted in an increase in PFS (all participants) compared to chemotherapy (HR 0.45, 95% CI 0.40 to 0.52)(six RCTs, 1611 participants, high-certainty evidence). This was found regardless of line of treatment.

Patients with CNS disease
ALK inhibitors improved PFS in patients with CNS disease compared to chemotherapy (HR 0.51, 95%CI 0.41 to 0.62). (six RCTs, 581 participants)

- **Overall Survival**

They found ALK inhibitors slightly improved OS compared to chemotherapy (HR 0.84, 95% CI 0.72 to 0.97)(six RCTs, 1611 participants, high-certainty evidence)

- **Overall Response Rate**

All participants
They found the ALK inhibitors were likely to increase ORR compared to chemotherapy (RR 2.43, 95% CI 2.16 to 2.75) (six RCTs, 1611 participants, moderate-certainty evidence)

Patients with CNS disease
ALK inhibitors improved ORR including in measurable baseline brain metastases (RR 4.88, 95% CI 2.18 to 10.95)(three RCTs, 108 participants)

- **Health Related Quality of Life (HRQoL)**

They found ALK inhibitors resulted in a large increase in the HRQoL measured (HR 0.52, 95% CI 0.44 to 0.60),(five RCTs, 1504 participants, high-certainty evidence), compared to chemotherapy.

- **Adverse Event**

They found ALK inhibitors resulted in no difference in overall AE rate, compared to chemotherapy (RR 1.01, 95%CI 1.00 to 1.03)(five RCTs, 1404 participants, low-certainty evidence).They found similarly there was no difference in Grade 5 AE between ALK inhibitors and chemotherapy, (RR 2.03, 95%CI 0.89 to 4.66) (six RCTs, 1611 participants, low-certainty evidence).They concluded the ALK inhibitors improved PFS, OS, ORR and HRQoL in comparison to chemotherapy, with similar overall AE rates.[17 level I]

ALK inhibitor versus chemotherapy or crizotinib

Breadner et al. (2020) in another SR of RCT assessed the efficacy (influence on OS and PFS, tumour response rates) and toxicity of ALK inhibitors compared to chemotherapy (ALK vs. chemo) and second generation ALK inhibitors compared to first generation ALK inhibitors (ALK-2 G vs. ALK-1 G). The review included ten RCTs (2583 patient), whereby six trials were comparing ALK vs chemotherapy, and four trials compared the second generation ALK inhibitor, ALK-2 G vs the first generation, ALK-1 G.

The ten trials were mixed in the treatment setting, with six trials (first line treatment setting), one trial (first- or second-line setting) and three trials (second line or later). Population of this SR were patients with advanced or metastatic ALK positive NSCLC. Systematic search was done from the electronic databases Medline (PubMed), EMBASE, and the Cochrane Database of Systematic Reviews were searched for relevant randomised trials published between January 1st, 2005 and September 10th, 2019. The primary outcome was OS (median OS) defined as the time from randomization to death from any cause. The secondary outcomes were median PFS, objective response rate (ORR). PFS was defined as the time from randomization to first documented disease progression, or death from any cause. ORR was defined as percentage of patients who attain a complete response (CR) or partial response (PR) as determined by the investigator or ICR using RECIST criteria version 1.1. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. Pooled hazard ratios (HR) for OS and progression free survival (PFS), and pooled risk ratios for objective response rates (ORR) and toxicity were meta-analysed using the generic inverse variance and the Mantel-Haenszel methods. To account for between-studies heterogeneity, random-effect models were used. Subgroup analyses compared PFS by gender, smoking status, brain metastases, race and age. The SR was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The risk of bias in the included studies was assessed using the Cochrane Collaboration risk of bias tool. Level of evidence for the pre-specified outcomes of interest was assessed and reported as low, moderate or high based on the GRADE approach.

- **Overall Survival**

They found treatment with ALK inhibitors improved OS compared to chemotherapy **(HR 0.84, 95 %CI 0.72 to 0.97)** (6 trials, 1623 patients).

A trend toward a better OS was seen with ALK-2 G vs ALK-1 G (HR 0.66, 95 %CI 0.43 to 1.02), (4 trials, 972 patients).

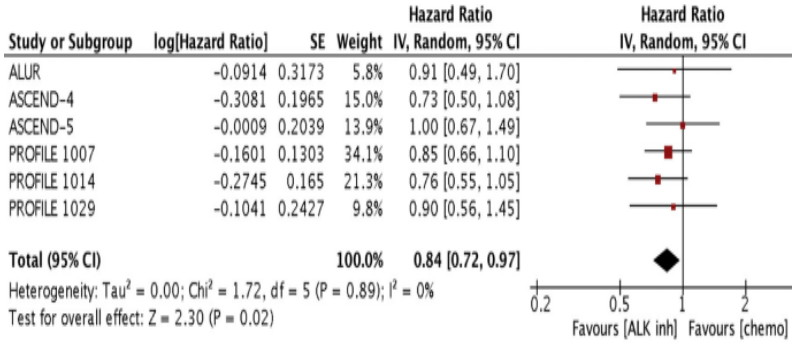


Figure 8: Forest plot of OS for 1st generation ALK inhibitor vs chemotherapy
Source: Breadner et al (2020)

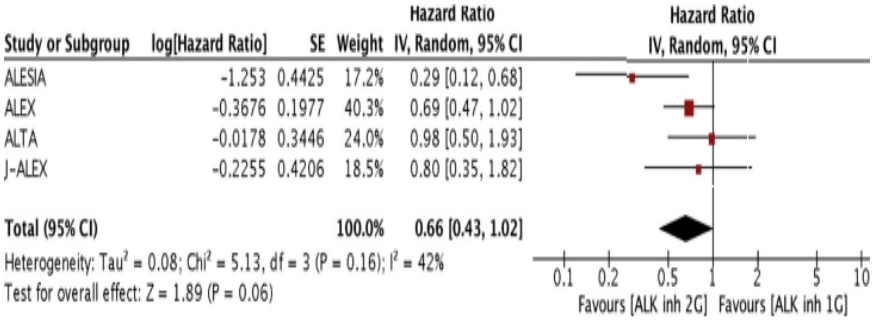


Figure 9: Forest plot for OS comparing ALK-2G vs ALK-1G
Source: Breadner et al (2020)

- **Progression Free Survival**

ALK inhibitor improved PFS vs. chemo, and similarly ALK-2 G improved PFS against the first generation (**HR 0.44, 95 %CI 0.35 to 0.54, HR 0.38, 95 %CI -0.29 to 0.51**) respectively.

- **Overall Response Rate**

The review found ALK inhibitor improved ORR compared with chemo and ALK-2 G vs. ALK-1 G, (**RR 2.74; 95 % CI 1.90 to 3.95) and (RR 1.16; 95 % CI 1.08 to1.24**) respectively.

- **Toxicity**

In terms of toxicity, the review found the risk of grade 3 or higher toxicity was not significantly different, comparing either ALK inhibitors to chemotherapy, or second generation ALK inhibitors to crizotinib (RR 1.08; 95 % CI 0.88 to 1.33) and (RR 0.77; 95 % CI 0.56 to 1.0) respectively.

They concluded there was an OS and PFS benefit with the use of ALK inhibitors compared to chemotherapy from randomised trial data. A trend toward a better OS was seen with second generation ALK inhibitor compared to the first generation. Longer follow up and further research are warranted to directly compare ALK inhibitor sequences and to understand the outcomes of second generation ALK inhibitors as initial therapy. [35 level I]

Zhao B et al. (2021) in another NMA aimed to compare the efficacy of current therapies on ALK-positive, brain metastatic (BM) NSCLC and determine proper therapeutic rankings; overcome the limitations of head-to-head comparisons and make recommendation based on the findings. The NMA included 11 RCTs (2687 NSCLC and 991 BM patients) investigating seven treatments (pemetrexed/ docetaxel, peme/cisplatin, crizotinib, ceritinib, alectinib, brigatinib, lorlatinib). Study selection was those studies involving adult patients (≥18 years) whose ECOG status was 0 or 1 with histologically or cytologically confirmed ALK-positive NSCLC including advanced stage (stage III/IV/recurrent/distant metastasis (brain, liver, bone, etc.)) and other stages were initially selected. Their life expectancy was no less than three months. The BM data were of particular interest. Trials were identified via search from PubMed, EMBASE, Cochrane Library and Clinical Trials.gov from inception up to April 20, 2021. Primary outcomes were PFS and ORR for brain metastatic (BM) patients; PFS and OS of all patients. OS for BM patients was not analysed given the limited data (only one study provided this information). Mean participants follow-up was 21.6 months. Progression-free survival (PFS), ORR and OS for the intended populations were analysed with random effects Bayesian NMA with the estimated HR and OR with 95% credible interval (95% CrIs). The surface under the cumulative ranking curve (SUCRA) metric was used to identify the relative effectiveness of each treatment and the best treatments. If the SUCRA value was close to 1, it was the best without uncertainty, close to 0, it was the worst without uncertainty. Calculations were performed in R software (version 3.5.3, www. r-project.org) with the publicly available gemtc and rjags packages.

All NSCLC patients

- **Progression Free Survival**

For PFS for all NSCLC patients, the top-ranking individual treatments was lorlatinib, followed by the others, as the table below.

Table 8: Rank of individual treatment (SUCRA) for PFS (all NSCLC patients)

Drugs	SUCRA value
Lorlatinib	0.976
Alectinib	0.795
Brigatinib	0.722
Crizotinib	0.450
Ceritinib	0.385
Peme/Doc	0.122
Peme/Cis	0.049

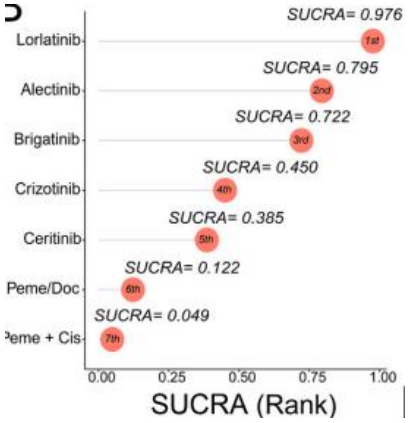


Figure 10: Diagram of SUCRA value (for PFS) for all NSCLC patients
Source: Zhao B et al (2021)

These were the corresponding HR respectively, for lorlatinib (HR 0.05, 95% CrI: 0.02 to 0.13), alectinib (HR 0.09, 95% CrI: 0.05 to 0.18) and brigatinib (HR 0.11, 95% CrI: 0.05 to 0.28).

- **Overall Survival**

For OS for all NSCLC patients, the following top-ranking interventions was alectinib, followed by the others as in the table below.

Table 9: Rank of individual treatment (SUCRA) for OS (all NSCLC patients)

Drug	SUCRA value
Alectinib	0.846
Lorlatinib	0.669
Ceritinib	0.479
Brgatinib	0.442
Crizotinib	0.365
Chemotherapy	0.200

These were the corresponding HR respectively for alectinib (HR 0.29, 95% CrI: 0.03 to 1.68), lorlatinib (HR 0.41, 95% CrI: 0.04 to 4.13) and ceritinib (HR 0.63, 95% CrI: 0.10 to 4.25).

Patients with Brain Metastasis NSCLC

- **Progression Free Survival**

For PFS in patients with BM, the top-ranking treatment was lorlatinib, followed by the others as shown below.

Table 10: Rank of individual treatment (SUCRA) for PFS (patients with BM)

Drugs	SUCRA value
Lorlatinib	0.973
Alectinib	0.775
Brigatinib	0.727
Ceritinib	0.395
Crizotinib	0.392
Peme/Cis	0.119
Peme/Doc	0.118

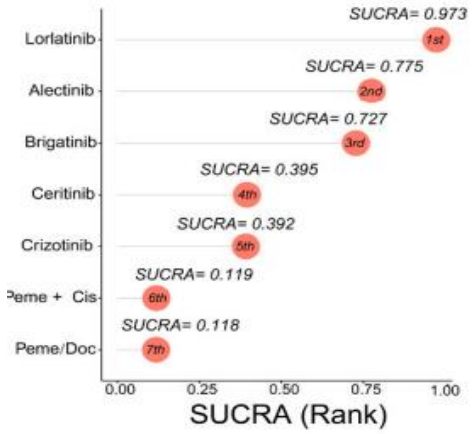


Figure 10: SUCRA value of individual ALK inhibitor for PFS in patients with BM

These were the corresponding HR, lorlatinib (HR 0.01, 95%CrI 0.001 to 0.12), alectinib (HR 0.05, 95%CrI 0.01 to 0.21) and brigatinib (HR: 0.07, 95%CrI 0.007 to 0.76)

- **Objective Response Rate (ORR)**

They found for ORR in patients with BM, the top-ranking treatment was brigatinib, followed by the others, as shown below.

Table 11: Rank of individual treatment (SUCRA) for ORR (patients with BM)

Drugs	SUCRA value
Brigatinib	0.824
Lorlatinib	0.792
Alectinib	0.699
Crizotinib	0.479
Ceritinib	0.161
Chemotherapy	0.045

The author's concluded there was statistical superiority of lorlatinib for patients with BM over other interventions. Alectinib was recommended as the first-line treatment, followed by lorlatinib, when patients develop drug resistance to alectinib. These findings may guide clinical decision-making, preferably be confirmed with OS as well as intracranial results in the future. [36 level I]

Elliott et al. (2020) in another NMA assessed the relative effects of individual ALK inhibitors for the treatment of NSCLC. The NMA included 13 RCTs; 7 RCTs compared ALK inhibitor to chemotherapy, and six RCTs involved head-to-head comparison of one ALK inhibitor to another ALK inhibitor, or to the same inhibitor at a different dose. In total, eight RCTs (crizotinib), five (alectinib), and two each (ceritinib, brigatinib). The size of the included study varies, between 28 and 376 participants with ALK-positive NSCLC. No RCTs involved participants with ROS1 NSCLC. Systematic search from the MEDLINE, Embase, Cochrane CENTRAL, and grey literature were done up to July 23, 2019 for studies that included participants with ALK- or ROS1-positive NSCLC who received any ALK inhibitor compared with placebo, another ALK inhibitor, or the same ALK inhibitor at a different dose. The primary outcome was treatment-related death. Secondary outcomes were overall survival (OS), progression-free survival (PFS), and serious adverse events. Data were pooled via meta-analysis and network meta-analysis, and risk of bias was assessed using Cochrane ROB tool for RCT. Pair-wise MA done to explore effect of any ALK inhibitor vs chemotherapy, then NMA to explore individual ALK inhibitor effect. Analysis was stratified by patient experience. Bayesian MA and NMA were performed using WinBUGS. Study selection follows this eligibility criteria, population: treatment naïve or experienced patients in phase III/IV ALK and/or ROS positive NSCLC. Intervention were ALK inhibitors (crizotinib, ceritinib, alectinib, brigatinib, loratinib).

- **Progression Free Survival**

Compared to chemotherapy

Any ALK inhibitors improved PFS with respective *hazard ratio, HR (95% CrI):*
crizotinib (HR 0.46 [95%CrI 0.39 to 0.54]); ceritinib (HR 0.52, 95%CrI 0.42 to 0.64); alectinib 300mg BID (HR 0.16, 95%CrI 0.08 to 0.33); alectinib 600mg BID (HR 0.23, 95% CrI 0.17 to 0.30); brigatinib (HR 0.23, 95%CrI 0.15 to 0.35).

The NMA found ALK inhibitors improved PFS similarly in both groups:-

- Treatment experienced (HR 0.47,95%CrI 0.41 to 0.53)
- Treatment naïve (HR 0.47, 95%0.39 to 0.57).

Comparison among ALK inhibitors

They found alectinib and brigatinib improved PFS over crizotinib and ceritinib with these corresponding *Hazard Ratio [95% CrI]):*
alectinib vs crizotinib (HR 0.34, 95%CrI 0.17 to 0.70); alectinib vs ceritinib (HR 0.30 95%CrI 0.14 to 0.64); brigatinib vs crizotinib (HR 0.49, 95%CrI 0.33 to 0.73); and brigatinib vs ceritinib (HR 0.43, 95%CrI 0.27 to 0.70), respectively.

- **Overall Survival**

In this review, they found OS improved with alectinib compared to:
- Chemotherapy, HR 0.57 (95%CrI 0.39 to 0.83)
- Crizotinib, HR 0.68 (95% CrI 0.48 to 0.96).

- **Adverse Event**

Compared with chemotherapy, the use of any ALK inhibitor was associated with an increased risk of SAE (OR 1.67, 95%CrI 1.34 to 2.08), I^2 62% among all patients. Result was consistent among both treatments experienced participants (OR 1.75, 95%CrI 1.23 to 2.46, I^2 73%) and naïve participants (OR 1.42, 95%CrI 1.10 to 1.89, I^2 18%).

Compared with chemotherapy, the use of these ALK inhibitors increased risk of SAE. Crizotinib (OR 2.08, 95% CrI 1.56 to 2.79), and alectinib (OR 1.60, 95%CrI 1.00 to 2.58), but not ceritinib (OR 1.25, 95%CrI 0.90 to 1.74). Among ALK inhibitors, ceritinib was associated with fewer SAE compared with crizotinib (OR 0.60, 95%CrI 0.39 to 0.93). Results were generally consistent among treatment-experienced or naïve participants.

They concluded among patients with ALK positive NSCLC, PFS was improved with crizotinib, ceritinib, brigatinib and alectinib. OS was improved by alectinib.[37 level I]

Petrelli F et al. (2018) in another SR assessed the efficacy of ALK inhibitors on patients with NSCLC with brain metastasis (BM). Systematic search was performed using Pubmed, EMBASE, Web of Science, The Cochrane Library, and SCOPUS up to 30 June 2017. Quality of trials was assessed by the Jadad scale for RCT and using the Newcastle-Ottawa Scale (NOS) for retrospective cohort studies. The primary endpoint was IC ORR. Data on IC ORR and intracranial disease control rate (IC DCR) were pooled that reflected the proportion of patients with complete response, partial response, or stable disease for at least 24 weeks. Secondary endpoints were IC DCR, median PFS, median OS, and one-year OS. Intracranial tumour response was assessed through overall response rate (ORR), disease control rate (DCR equals to ORR plus stable disease rate), median progression-free survival (PFS), and overall survival (OS).

The review included 21 studies (1,016 patients with ALK positive NSCLC and BMs), comprised of 11 RCT and ten retrospective studies. The included studies evaluated crizotinib (7), ceritinib (5), alectinib (4), crizotinib and alectinib (1), brigatinib (2), and not specified (2). Outcomes for intracranial ORR, DCR, PFS, as well as median OS, median PFS and one-year OS were as below.

- **Intracranial ORR**

First line (naive patients)
They found in patients receiving ALK inhibitors in the first line setting, the pooled IC ORR was 39.17% (95%CI 13.1 to 65.2%),(three studies).

Second line (pre-treated patients)
In patients receiving ALK inhibitors in further lines setting, the pooled IC ORR was 44.2% (95%CI 33.3 to 55.1%)(12 studies).

- **Intracranial disease control rate (DCR)**

First line (naïve patients)
They found in patients receiving ALK inhibitors in the first line setting, the pooled IC disease control rate was 70.3% (95%CI 47.7 to 86.0%)(three studies).

Second line (pre-treated patients)
In patients receiving ALK inhibitors in further lines setting, the pooled IC DCR was 78.2% (95%CI 70.0 to 85.9%)(nine studies).

- **Intracranial ORR (post brain radiation)**

In this review, patients who had not received brain radiation attained an intracranial ORR of 49.0%.

- **Intracranial PFS, Median PFS, Median OS, 1-year OS**

The intracranial PFS, median PFS and one-year OS were slightly lower in naïve compared to pre-treated patients with ALK inhibitors.[38 level I]

Table 12: Intracranial PFS, Median PFS, Median OS, 1-yr OS among the naïve and pre-treated patients

Patients	Outcome	Value (Range)
Naive	Med PFS	7.3month (5.9 to 10.7)
	Med ICPFS	13.2month (7.0 to 15.7)
	Med OS	23month
	1-yr OS	64% (59.0 to 81.0%)
Pre-treated	Med PFS	8.0month (4.4 to 38.0)
	Med ICPFS	14.6month (8.0 to 22.3)
	Med OS	23month
	1-yr OS	71.4%

Alectinib versus crizotinib

Zeng Q et al. (2022) in another SR aimed to compare the efficacy and safety of crizotinib with those of alectinib for treatment of ALK-positive NSCLC. This review included seven articles involving 697 ALK positive NSCLC patients (380 in alectinib arm, 317 in crizotinib arm, with median age (range) of 55 (49 to 61) and Eastern Cooperative Oncology Group (ECOG) status 0 to 2. The ALEX (multicountries), ALESIA (Asia) and J-ALEX (Asia) were among the included studies. The length of

follow-up was between 15 to 42.4 months. They included studies evaluating alectinib 300mg bd (three studies) and alectinib 600 mg bd (six studies), versus crizotinib.

In this review, systematic search was done from these databases (PubMed, EMBASE, Scopus, Ovid MEDLINE, Web of Science, the Cochrane Library, ScienceDirect) for relevant articles up to 5 March 2021.The primary endpoints were OS, PFS, central nervous system (CNS)-PFS, drug responses, and AE. In addition to analyzing the time-to-event data, the rates of survival (OS rate [OSR], PFS rate [PFSR], and CNS-PFS rate [CNS-PFSR]) at 6, 12, 18, 24, and 30 months (OSR 6 to 30 months, PFSR 6 to 30 months, and CNS-PFSR 6 to 30 months) between the two groups were compared. Quality of included RCTs was assessed using the 5-point Jadad scale and the Cochrane Risk Assessment Tool. Review Manager 5.3 software (Nordic Cochrane Center, Oxford, UK) was used to pool the data. Hazard ratio (HR) was used to analyze the survival data (OS, PFS, and CNS-PFS), while risk ratio (RR) used to analyze the dichotomous variables (drug responses, OSR, PFSR, CNS-PFSR, and AE).

- **Progression Free Survival**

They found PFS was better in the alectinib group compared with crizotinib group, (HR 0.35, 95%CI 0.25 to 0.49), (three studies, I^2 56%). The PFSR at all time points were significantly favoured alectinib, as table 13 below.

Table 13: PFS rate at different time points for alectinib vs crizotinib

Time points	PFS rate (RR)	95%CI
6 months	0.87	0.81 to 0.95
12 months	0.63	0.55 to 0.72
18 months	0.51	0.43 to 0.62
24 months	0.38	0.27 to 0.53
30 months	0.39	0.27 to 0.56

- **Overall Survival**

They found alectinib improved OS, as compared with crizotinib in the study population, (HR 0.66, 95%CI 0.47 to 0.92)(3 studies, I^2 55%). In terms of OS rate at different time points, the OS rate tend to favour alectinib, but not significant.

Table 14: OS rate at different time points for alectinib vs crizotinib

Time points	OS rate (RR)	95%CI
6 months	0.97	0.91 to 1.04
12 months	0.89	0.79 to 1.02
18 months	0.83	0.68 to 1.00
24 months	0.74	0.50 to 1.09
30 months	0.76	0.52 to 1.11

- **CNS-PFS**

The review found CNS-PFS was better in alectinib group compared with crizotinib group (HR 0.17, 95% CI 0.11 to 0.24)(3 studies, I^2 0%). The CNS-PFS at different time points were significantly favoured alectinib compared to crizotinib.

Table15 :CNS-PFS rate at different time points for alectinib vs crizotinib

Time points	CNS-PFS rate (RR)	95%CI
6 months	0.88	0.80 to 0.96
12 months	0.70	0.64 to 0.76
18 months	0.66	0.60 to 0.73
24 months	0.58	0.51 to 0.66
30 months	0.58	0.47 to 0.72

- **Duration of response**

The duration of response was better in alectinib compared with crizotinib group (HR 0.31, 95%CI 0.23 to 0.42)(three studies, I^2 0%).

- **Objective Response Rate**

The objective response rate (ORR) was better in alectinib compared with crizotinib group (risk ratio [RR] 0.87, 95%CI 0.80 to 0.94) (three studies, I^2 0%).

- **Partial response**

In terms of partial response, it was better in alectinib group compared with crizotinib group (RR 0.88, 95%CI 0.81 to 0.96).

- **Adverse Event**

Crizotinib was associated with more grade 3 to 5 AEs (RR 1.43, 95%CI 1.09 to 1.87) compared with alectinib. These AE were comparable between the 2 groups, as described in Table 16.

Table 16: Summary of AE comparing alectinib and crizotinib

AE	Incidence of AE (%) crizotnib vs alectinib	RR (95%CI)
Total AE	98.7% vs 98.1%	1.01 (95%CI 0.99 to 1.03)
Serious AEs	29.0% vs 24.4%	1.12 (95%CI 0.88 to 1.44)
Fatal AEs	3.1 % vs 2.1%	1.51 (95%CI 0.62 to 3.69)
AEs leading to treatment discontinuation	15.7% vs 10.7%	1.37 (95%CI 0.93 to 2.02)
AEs leading to dose reduction	21.1% vs 19.8%	1.11 (95%CI 0.77 to 1.60)
AEs leading to dose interruption	39.4% vs 26.5%	1.38 (95%CI 0.90 to 2.12)
Death	0% vs 0.53%	0.20 (95%CI 0.01 to 4.16)

The crizotinib group reported higher rates of constipation, nausea, diarrhoea, vomiting, peripheral oedema, dysgeusia, visual impairment, and levels of alanine aminotransferase and aspartate aminotransferase as well as greater decreases in appetite and neutrophil count.

They concluded alectinib exhibited superior efficacy in PFS, OS, CNS-PFS, ORR and partial response compared with crizotinib. In both antitumor efficacy and safety, alectinib appears to be superior to crizotinib for the treatment of ALK-positive NSCLC. 39 level I

Tang H et al. (2021) in another SR of RCT evaluated the efficacy and safety of alectinib versus crizotinib in the treatment of ALK positive non-small-cell lung cancer. The review included three studies (comprising a total of 697 patients with ALK positive with advanced NSCLC (stage IIIB or IV), ECOG 0-2 points), n=380 in the alectinib group and n=317 in the crizotinib group. The length of follow up was from 17.6 to 42.4 months. Search was conducted for studies about the efficacy of alectinib versus crizotinib in the treatment of ALK positive non-small cell lung cancer in PubMed, Scopus, Embase and the Cocharane Library from inception to February 15, 2020. Two reviewers independently screened these studies, extracted the data, assessed the risk of bias in the included studies by using the Cochrane risk assessment tool, and then used review manager 5.3 software for meta-analysis. Outcomes were Overall response rate (ORR), progression-free survival (PFS), disease control rate (DCR), complete response (CR), partial response (PR), stable disease (SD) and adverse events (AEs).

They found alectinib was superior than crizotinib in PFS (HR 0.34, 95% CI 0.21 to 0.55) (3 studies, I^2 76%), Overall Response Rate (ORR) (OR 2.07, 95% CI 1.41 to 3.06) (3 studies, I^2 0%) and Partial Response (OR 1.71, 95% CI 1.19 to 2.46) (3 studies, I^2 10%). However, there was no difference between alectinib and crizotinib in Disease Control Rate (OR 2.24, 95%CI 0.56,8.88)(3 studies, I^2 76%), Complete Response (OR 1.82, 95%CI 0.75,4.45)(3 studies, I^2 0%) and grade 3-5 AE (OR 0.50, 95%CI 0.23 to 0.81)(3 studies, I^2 53%).They concluded that alectinib in terms of ORR, PFS and partial response is superior to crizotinib in the treatment of ALK positive NSCLC and is well tolerated. Compared with crizotinib, alectinib is more effective and has a lower incidence of total adverse reaction. 40 level I

Yang Y et al. (2020) in another SR evaluated the efficacy of alectinib and crizotinib on progression-free survival (PFS), central nervous system (CNS) progression and adverse events (AEs) in NSCLC patients with ALK-positive. Systematic search was done for relevant literature in these databases, PubMed, EMBASE, Cochrane Library, and Web of Science up to 30 April 2019. The hazard ratio (HR) was calculated, and the effect of alectinib and crizotinib on PFS was evaluated. Pooled estimates of cumulative incidence of CNS progression in patients treated with alectinib at the 6th and 12th months and 95% confidence interval (CI); and combined incidence of AE grade ≤2 and AE grade ≥3 were evaluated. The quality of the studies was assessed using the Cochrane Risk of Bias tool. Publication bias was assessed using Begg rank correlation test and the Egger weighted linear regression test. All analyses were

performed in STATA. The review included ten studies, with total participants of 2,377 (range 46 to 1221), of which four studies were RCTs, and six studies were prospective or retrospective cohort studies. The included studies were conducted in Japan, USA, Germany and multicountries study.

- **Progression Free Survival**

Alectinib showed significant PFS superiority compared to crizotinib, (HR 0.41, 95% CI 0.29 to 0.53)(3 studies).

- **Incidence of CNS progression**

The cumulative incidence of CNS progression for patients treated with alectinib was 10% (95% CI 5 to 16%) at 6 months and 16% (95% CI 9 to 24%) at 12 months (5 studies).

- **Adverse Event**

Alectinib was associated with 28 cases of AE grade ≤2 and 9 cases of AE grade ≥3 (based on 7 studies). The highest incidence of grade 1-2 AE were fatigue (24.7%), GI disorders (21.8%), dysgeusia (20.3%), AST increased (14.1%), peripheral oedema (13.7%). While the top four incidences of AE grade ≥3 were increase in Creatine phosphokinase (5.6%), increase in ALT (2.5%), increase in AST (2.4%), and anaemia (1.8%).They concluded alectinib significantly prolong PFS and better control CNS metastases than crizotinib with good toxicity characteristics in its use in the first-line treatment of ALK positive NSCLC patients. This review provides references for the clinical use of alectinib.[41 level I]

Ceritinib

Zhao X et al. (2018) in another SR aimed to determine the whole body and intracranial effectiveness and safety of ceritinib in crizotinib-naive versus crizotinib-pretreated regimens in ALK-rearrangement NSCLC. They conducted comprehensive search of databases, including PubMed, EMBASE, Ovid, Web of Science, and COCHRANE, was performed to identify trials in English-language journals up to August 2017. Studies were included if they had assessed effectiveness and safety of ceritinib for ALK-rearrangement NSCLC or metastases to the brain with crizotinib-naive versus crizotinib-pretreated patients. Data were pooled statistically using event rates calculated for the primary endpoints, including mean PFS duration, ORR, intracranial DCR, partial response, and complete response. Secondary endpoints included toxicity and dose reduction or cessation because of ceritinib AE. The pooled progression-free survival (PFS) and overall response rate (ORR), intracranial disease control rate (DCR) for ceritinib in whole body and intracranial responses was estimated to find differences between crizotinib-naive and crizotinib-pretreated regimens. ORR was defined as the proportion of patients with a best overall confirmed response of a complete or partial response since the date of ceritinib. PFS was defined as the interval between the first intake of ceritinib and the first occurrence of disease progression or death from any cause during the study, whichever occurred first, in the whole body. DCR was defined as the percentage of participants who had attained a complete response, partial response, or stable disease for ≥5 weeks. Study quality was evaluated using the Effective Public Health Practice Project Tool (EPHPP).)

The review included seven studies (1015 participants) from phase I, II and III trials published between 2014 and 2017. Of these studies, four had described ceritinib for crizotinib-naive patients and the other three for crizotinib-pretreated patients. Participants mean age (range) was 52.7(45.5 to 56.0) years old. Status of brain metastasis among the participants was between 31% and 79%, with ECOG PS Score ≤1 (6% and 87%).

- **ORR**

They found the pooled ORR was 56.9% (95% CI 53.6% to 60.1%),(7 studies, I^2 80.4%).The pooled ORR was better for ceritinib in **crizotinib naïve** compared with crizotinib-pretreated (ORR of 68.9% (95%CI 64.3% to 73.1%) vs 48.2% (95% CI 43.8% to 52.7%) respectively, (five studies, I^2 23.6%).

- **Progression Free Survival**

They found the pooled PFS was 8.2 months (95% CI, 6.18 to 11.07 months) following ceritinib. The pooled PFS was longer for ceritinib in **crizotinib naïve** compared with crizotinib-pretreated group (14.6 months (95%CI 11.9 to 17.8 months) vs (6.32 months (95%CI 5.6 to 7.1 months) (five studies, I^2 37.2%).

- **Effect on brain metastasis**

Intracranial ORR
They found the pooled Intracranial ORR following ceritinib was 41.3% (95% CI, 35.3% to 47.6%); (four studies, I^2 41.3%).

Intracranial disease control rate (DCR)
Following ceritinib, the pooled intracranial DCR was 79.8% (95% CI, 73.8% to 84.7%), (four studies, I^2 49.2%).

The intracranial ORR was higher for ceritinib in crizotinib naïve (50.6%) compared with crizotinib-pretreated(33.6%).

- **Adverse Event**

The rate of treatment discontinuation due to an AE was 3.1% (95% CI, 1.4% to 7.1%). The dose reduction rates was 38.4% (95% CI 19.0% to 62.4%). Most AE were grade 1 or 2, small proportion were grade 3 or 4 AE. The most common grade 3/4 AE were increase alanine aminotransferase (25.5%), increase g-glutamyltransferase (12.6%), and increase in aspartate aminotransferase (11.1%). They concluded ceritinib is an effective agent for both crizotinib-naive and crizotinib-pretreated patients with locally advanced or metastatic ALK-rearranged NSCLC. The findings support the use of ceritinib ALK-rearranged NSCLC patients with brain metastases, particularly in crizotinib-naïve patients. [42 level I]

5.2.4 Safety

Five SR were retrieved specifically addressing safety of ALK inhibitors in the ALK positive NSCLC patients. Another seven SR evaluated both effectiveness and safety of ALK inhibitors in these patients as documented in the earlier section.

Cirne et al. (2021) conducted SR to determine the risk of bradycardia associated with ALK inhibitors in patients with advanced NSCLC. Systematic search was done from MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, National clinical trial registry, and Web of Science Core Collection up to February 2021. All RCTs in which an ALK inhibitor was compared with another ALK inhibitor or standard chemotherapy were included. Meta-analysis was performed using a fixed effects model. The methodological quality of the studies was assessed using Cochrane Collaboration risk of bias tool by two reviewers. The review included 12 RCTs consisting of 2915 NSCLC patients who were prescribed ALK inhibitors, with age range of 48.2 to 61 years. Length of follow-up was up to 1.26 years. The intervention evaluated were crizotinib 250mg bd (four studies), ceritinib 750mg od (two studies), alectinib 600mg bd (four studies), lorlatinib (one study) and brigatinib 180mg od (one study), versus either chemotherapy or crizotinib.

- **Bradycardia**

The pooled incidence of bradycardia among 1737 individuals prescribed ALK inhibitors was 8% during a mean follow-up of 1.26 years. Compared to standard chemotherapy, crizotinib led to more bradycardia (relative risk,RR 24.68, 95% CI 7.11 to 85.), while no difference in the risk of bradycardia was seen between crizotinib and alectinib (RR 1.12, 95% CI 0.79 to 1.59). There were insufficient studies to evaluate the next-generation ALK inhibitors (alectinib, brigatinib, and lorlatinib) individually. However, when the three drugs were considered as a group, there was a similar rate of bradycardia when compared to crizotinib (RR 0.77, 95% CI 0.57 to 1.04). They concluded crizotinib for the treatment of NSCLC is associated with a higher risk for bradycardia compared to standard chemotherapy. There is no evidence of a difference in bradycardia risk between crizotinib and newer ALK inhibitors

- **Dizziness**

All ALK inhibitors (as a group) caused more dizziness than standard chemotherapy (RR 1.88, 95% CI 1.44 to 2.44). Crizotinib caused more dizziness than standard chemotherapy (RR 2.18, 95% CI 1.59 to 3.00). Alectinib caused less dizziness than crizotinib (RR 0.45, 95% CI 0.28 to 0.73), while ceritinib had similar rates of dizziness compared to standard chemotherapy (RR 1.41, 95% CI 0.86 to 2.32).. [44 level I]

Costa RB et al. (2018) in another SR evaluated the side effect of ALK inhibitors in NSCLC with a focus in selected adverse events. Systematic search done from PubMed, EMBASE, Cochrane Library, and MEDLINE up to July 2017. All RCTs in which an ALK inhibitor was compared with another ALK inhibitor or standard chemotherapy were included. Studies evaluating US FDA-approved doses of one of the following ALK inhibitors: Crizotinib, Ceritinib, Alectinib or Brigatinib as monotherapy were included. Data were analyzed using random effects meta-analysis for absolute

risks (AR), study heterogeneity, publication bias, and differences among treatments. The review included 15 studies consisting of 2005 NSCLC patients, with median age: 54.6 years, all of the patients had either stage IIIB or stage IV disease.

- **Toxicity rates**

Toxicity rates for any AE, any serious AE, and grade 3/4 AE were as follows:
98.4% (95% CI 96.9 to 99.2), 34.5% (95% CI 28.1 to 41.6), and 64% (95% CI 47.1 to 78), respectively. There was significant inter-study heterogeneity for most toxicities; any AE (I^2: 36.5%), any serious AE (I^2:82.6%), and grade 3 to 4 AE (I^2:96.1%). The pooled AR of discontinuation for all four ALK inhibitors (Crizotinib, Alectinib, Ceritinib, Brigatinib) due to toxicity was approximately 8.2%.

- **Treatment-related death**

They found less than 0.5% of the pooled population were reported to have treatment-related death (n=10). Cause of death: bowel perforation (n=1), unspecified haemorrhage (n=1),cardiac arrhythmia (n=1), interstitial lung disease/pneumonia (n=4), multiorgan failure (n=1), not specified (n=2).

- **Number of all-grade and grade 3/4 gastrointestinal (GI) and other toxicities**.

The most common GI toxicities were diarrhoea, nausea, vomiting, and constipation. Estimated AR for all grade toxicities; diarrhoea 54% (95% CI 41 to 68), nausea 52% (95% CI 40 to 63), vomiting 38% (95% CI 29 to 48) and constipation 32% (95% CI 27 to 36). The risk for grade 3/4: diarrhoea 2.6% (95% CI 2 to 4); nausea 2.5% (95% CI 2 to 4); vomiting 2.7% (95% CI 2 to 4); constipation 1.2% (95% CI 1 to 2). Compared to other ALK inhibitors, ceritinib was associated with a high rate of nausea, vomiting and diarrhoea with a low chance of Grade 3/4 toxicity. The AR for all-grade fatigue was 27.2% with an AR for grade 3/4 fatigue of 3.2%. The risk for grade 3/4 QTcB prolongation was 2.1%.

They concluded ALK inhibitors have an acceptable safety profile with a low risk of treatment-related deaths. Important differences in toxicity profile were detected amongst the different drugs.[44 level I]

Li J et al. (2019) in another SR evaluated the overall risk of liver toxicity during the administration of ALK inhibitors. Systematic search was done from PubMed, EMBASE, and Cochrane Library up to January 2018. All published phase II and III clinical trials involving NSCLC patients who received ALK inhibitors were included. The outcome of interest was incidence rates of liver toxicities and relative risks (RR). Meta-analysis was performed using a fixed effects model. The quality of included trials was assessed using the Jadad scale. The review included 12 studies consisting of 2418 NSCLC patients, with age range from 49 to 64 years.

- **ALT increase**

The incidence of all-grade and grade 3 or 4 ALT elevation were 26.0% (95% CI 17.4% to 37%) and 8.4% (95% CI 5.1% to 13.4%).

The incidence of ALT was higher with ceritinib (56.4%, 95% CI 38.9% to 72.5%) compared to alectinib (13.3%, 95% CI 9.9% to 17.7%) and crizotinib (28.4%, 95% CI 18.8% to 40.5%). The RR to develop all-grade and grade 3 or 4 ALT increase compared to chemotherapy were 2.37 (95% CI 1.97 to 2.86) and 7.34 (95% CI 3.95 to 13.63), respectively.

- **AST increase**

The incidence of all-grade and grade 3 or 4 AST elevation were 23.2% (95% CI 16.7% to 31.4%) and 7.0% (95% CI 4.8% to 10.2%), respectively. The incidence of AST was higher with ceritinib (41.9%, 95% CI 23.3% to 63.1%) compared to alectinib (13.1%, 95% CI 9.0% to 18.6%) and crizotinib (26.3%, 95% CI 18.6% to 35.7%).The RR to develop all-grade and grade 3/4 of AST increase compared to chemotherapy were 3.27 (95% CI 2.47 to 4.34) and 11.54 (95% CI 4.33 to 30.7), respectively. They concluded ALK inhibitors treatment in advanced NSCLC significantly increases the risk of developing all-grade and high-grade liver toxicities in comparison with controls. Clinicians should recognize liver toxicities promptly as early interventions may alleviate future complications.[45 level I]

Kassem L et al (2019) in another SR described the exact safety profile of ALK inhibitors in NSCLC. Systematic search was done from PubMed, ASCO library, ESMO, IASLC, and ELCC databases from January 2005 to August 2017. All prospective clinical trials involving NSCLC patients who received ALK inhibitors were included. The outcome of interest was incidence rates of liver toxicities and relative risks (RR). The methodological quality of the studies was assessed using the Cochrane Collaboration risk of bias tool by two reviewers. The review included 14 studies consisting of 2793 patients with advanced NSCLC, age ranging from 48 to 61 years. Studies assessing crizotinib, ceritinib, alectinib and brigatinib compared to crizotinib or chemotherapy were included.

- **Gastrointestinal (GI) toxicities**

All grade nausea ranged from 10.7% to 83%. The incidence of nausea was highest with ceritinib (range: 66.0 to 88.3%) and was lowest with alectinib (range:10.7 to 21.8%).The incidence of all grade vomiting (range:4 to 67%) was highest with ceritinib (range:52-67%) and lowest with alectinib (range:4 to 11.5%). The incidence of all grade diarrhoea (range:4 to 68%) was also the highest with ceritinib (range:72 to 86%) and lowest with alectinib (range: 4 to 20.7%).Grade 3 or 4 GI toxicities were generally uncommon: nausea (0 to 8%), vomiting (0 to 8%) and diarrhoea (0 to 6.4%).Constipation occurred more with crizotinib and alectinib (range: 24 to 44.2%) than ceritinib and brigatinib (range:19 to 30%).

- **Hepatic toxicities**

The ALT and AST elevation (range: 10.7 to 60%) was more common in patients receiving ceritinib and crizotinib compared to alectinib and brigatinib. Grade 3 or 4 elevated liver enzymes were also more common in patients receiving ceritinib (range:3 to 31%).

- **Fatigue, visual disorder and peripheral edema**

The incidence of fatigue reported were: all grade (range:15 to 43%) and grade 3 or 4 (range:0 to 64%).The occurrence of visual disorders (diplopia, photopsia, blurred vision, visual impairment, and vitreous floaters) were only reported with crizotinib (range:54.8 to 82%).Peripheral oedema was reported in patients receiving crizotinib and alectinib (range: 25 to 49%).

- **Hematological toxicities**

Neutropoenia (all grade, range: 3.5 to 21% and grade 3 or 4: range: 0 to 13%) and anaemia (all grade, range: 12 to 18.3% and grade 3 or 4: range: 0 to 2%) were reported from included studies.

- **Miscellaneous toxicities**

The incidence of nasopharyngitis and dysgeusia were reported with crizotinib (10%) and alectinib (11 to 52%).

- **Serious Adverse Event & treatment-related death**

The most common serious AEs reported were dyspnoea (7%), pneumonia (7%), and hypoxia (5%). Treatment-related death was infrequent with ALK inhibitors (range:0-1%). Two treatment-related death were reported with alectinib due to haemorrhage and intestinal perforation, while two death with ceritinib were due to intestinal lung disease and multiorgan failure.They concluded most of the adverse effects of ALK inhibitors can be managed efficiently via dose modifications or interruptions. Timely identification of each ALK inhibitors pattern of toxicity can prevent treatment-related morbidity and mortality in this palliative setting.[46 level I]

Pellegrino et al. (2018) in another SR assessed the epidemiologic magnitude and the clinical significance of lung toxicity in NSCLC patients treated with ALK-TKIs. They searched MEDLINE, ESMO, ASCO, and WCLC database up to June 2017. All studies involving NSCLC patients who received ALK inhibitors were included. Descriptive statistics were used to summarize characteristic data of patients and tumors. The review included 53 studies (5653 participants). They found toxicities were reported for 4943 patients involved in 47 studies. Lung toxicity was reported in 105 of 4943 NSCLC patients (2.1%).Lung toxicity was observed in patients who received crizotinib (1.8%), ceritinib (1.1%), alectinib (2.6%) and brigatinib (7%).Grade 3/4 lung toxicity was reported in 65% patients, with a mortality rate of 9%.Pneumonia was reported in 25 patients with crizotinib (26%), brigatinib (52%), and alectinib (22%). Interstitial lung disease was reported in 37 patients with crizotinib (51.3%), ceritinib (18.9%), alectinib (27%) and lorlatinib (2.7%).Overall, 26 of 105 patients (25%) permanently discontinued treatment because of lung toxicity. They concluded lung toxicity is a rare albeit potentially severe side effect in NSCLC patients receiving ALK inhibitors, apparently more frequent with brigatinib. Its early recognition and treatment are crucial for the best outcome for this subgroup of patients, whose overall prognosis is being improved by the availability of several targeted agents.[47 level I]

5.2.5 Economic implication

There were 12 cost-utility analysis (CUA) studies retrieved and included in this review. The CUA were conducted in China (4), Hong Kong, Canada, US (3), France, Sweden and Greek from healthcare, provider, public healthcare, payer, collective payer and patient, and societal perspective. Findings from the included CUA was as summarized in the table below.

Table 17: Summary of findings from CUA included in the review

Study	Perspective	Comparison	ICER (Base case analysis)	Treatment setting/population
Peng Y 2019 *China*	Chinese healthcare perspective	Ceritinib vs chemo	$230,661/QALY (5year)	First line
Loong HH 2020 *Hong Kong*	Health service provider	Ceritinib vs chemo	$13,343/QALY	Previously untreated
Hurry M 2016 *Canada*	Public healthcare	Ceritinib vs chemo	$149,117/QALY (vs BSC) $80,100/QALY (vs perm) $104,436/QALY (vs HC)	Previously treated with crizotinib
Zhou 2018 *US*	Payer	Ceritinib vs crizotinib and chemo	$66,064/QALY (vs crizo) $81,645/QALY (vs chemo)	First line
Li H 2019 *China*	Chinese healthcare system	Ceritinib and alectinib vs crizotinib	$62,231/QALY (alec vs crizo) $13,905/QALY (ceri vs crizo)	Treatment naïve
Liu M 2019 *China*	Chinese Medical system	Ceritinib and alectinib vs crizotinib	$64,398/QALY (ceri) $102,675/QALY (alec)	First line
Carlson JJ 2018 *US*	Payer	Alectinib vs crizotinib	$39,312/QALY	Treatment naïve
Sivignon M 2020 *France*	Collective payer & patients	Alectinib vs crizotinib	€90,232/QALY ($107,759/QALY)	First line
Guan H 2019 *China*	China healthcare system	Alectinib vs crizotinib	$52,869/QALY	NA
Li S 2021 *US*	US payer	Lorlatinib vs crizotinib	$409/667/QALY	First line
Nilsson 2021 *Sweden*	Societal	Lorlatinib vs chemo	SEK566,278/QALY (2nd line) ($59,912/QALY) SEK603,934/QALY (3rd line) ($63,896/QALY)	Second/third line
Gourzolidis 2022 *Greek*	Payer	Lorlatinib vs chemo	€46,102/QALY (56,664/QALY)	Second/third line

Peng Y et al. (2019) conducted CUA on ceritinib and platinum based chemotherapy as first line treatment for advanced non-small cell lung cancer in China from the China healthcare perspective. The CUA aimed to evaluate the cost-effectiveness of ceritinib as a first-line treatment for advanced NSCLC with rearrangement of ALK. They found from the base-case analysis, compared with platinum-based chemotherapy, ceritinib would increase benefits (add an extra 0.33, 0.59 and 0.65 QALY) in a 5-, 10- and 15-year time horizon, and the ICERs were $230,661.61,$149,321.52 and $136,414.43 per QALY gained, respectively. Sensitivity analysis the most sensitive parameter in the model analysis was the cost of ceritinib, followed by utility of PFS, cost of permetrexed, body surface area and discount rate. Probabilistic sensitivity analysis suggested that at the current price of ceritinib, the chance of ceritinib being cost-

effective was 0 at the WTP threshold of $27,142.85 per QALY (three times the per capita gross domestic product of China). The authors concluded as a first-line treatment for advanced NSCLC with rearrangement of ALK, ceritinib is unlikely to be cost-effective at the current price from the Chinese healthcare perspective. To meet the treatment demands of patients, it may be a better option to reduce the price or provide appropriate drug assistance policies. [48]

Loong HH, et al. (2020) in another CUA conducted cost effectiveness analysis of ceritinib vs crizotinib in previously untreated ALK positive NSCLC in Hong Kong. The CUA aimed to examine the cost-effectiveness of ceritinib vs. crizotinib in the frst-line treatment of ALK+NSCLC from a HK healthcare service provider's or government's perspective.

They found in terms of clinical outcome; PFS (HR 0.64, 95%CI 0.47 to 0.87), Median PFS (25.2 vs 10.8 months), OS (HR 0.82, 95%CI 0.54 to 1.27) for ceritinib vs crizotinib respectively. In the base case analysis, ceritinib was associated with 3.22 QALYs, 4.51 LYs, and total costs of $157,581 over 20 years. Patients receiving crizotinib had 2.68 QALYs, 3.85 LYs, and $150,424 total costs over the same time horizon. The ICER for ceritinib vs crizotinib was $13,343 per QALY gained. In the sensitivity analysis, the results were most sensitive to the monthly drug costs for crizotinib and ceritinib, HR of PFS for crizotinib vs crizotinib, and assumption on treatment until progression. Results were robust to deterministic sensitivity analyses in most scenarios. They concluded, the greater LY and QALY as well as the longer PFS associated with ceritinib compared to crizotinib demonstrated ceritinib potential to offer greater clinical benefit to patients. Ceritinib offers a cost-effective option compared to crizotinib for previously untreated ALK+ advanced NCSLC in Hong Kong. [49]

Hurry M, et al. (2016) conducted another CUA on cost-effectiveness of ceritinib in patients previously treated with crizotinib in ALK positive (ALK+) NSCLC in Canada. The CUA aimed to assess the cost-effectiveness of ceritinib vs alternatives in patients who discontinue treatment with crizotinib in ALK-positive NSCLC from a Canadian public healthcare perspective. They found the clinical outcomes was as projected below:

Table 18: Projected median PFS and OS of ceritinib and crizotinib

Intervention	Median PFS (months)	Median OS (months)
Ceritinib	6.7	15.6
BSC	1.8	4.7
Permetrexed monotherapy	4.3	9.7
HC	1.3	1.7

From the base case analysis, over four years, ceritinib was associated with 0.86 QALYs and total direct costs of $89,740 for the positive ALK population. The ICER was $149,117 comparing ceritinib vs BSC, $80,100 vs pemetrexed, and $104,436 vs HC.

Table 19 : Base case results

Item	Ceritinib	BSC	Perm	HC
Total cost ($)	89740	10686	89740	17658
Total QALY	0.86	0.33	0.86	0.17
ICER/QALY	-	149,117	80,100	104,436

Sensitivity analysis and the result was most sensitive to the following: cost of ceritinib until treatment discontinuation, unit cost of ceritinib and dose intensity, unit cost of permetrexed, time horizon and parametric function (log normal distribution, log logistic distribution and Gompertz). They concluded, based on the WTP threshold for end-of-life cancer drugs, ceritinib may be considered as a cost-effective option compared with other alternatives in patients who have progressed or are intolerant to crizotinib in Canada. Ceritinib addresses the significant unmet need for a subgroup of NSCLC patients who harbour ALK gene rearrangement and provides a potential survival benefit, while aligning with patient values.

Zhou Z, et al (2018) in another CUA assessed cost-effectiveness of ceritinib in previously untreated ALK positive metastatic NSCLC in the United States. The CEA aimed to assess the cost-effectiveness of first-line ceritinib vs crizotinib and platinum doublet chemotherapy for ALK-positive metastatic non-small cell lung cancer (NSCLC) from a US third-party payer's perspective.

They found in the base case analysis:-

- First-line ceritinib was associated with total direct costs of $299,777 and 3.28 QALYs (from 4.61 life years gained [LYG]) over 20 years horizon.
- First-line crizotinib and chemotherapy were associated with 2.73 and 2.41 QALYs, 3.92 and 3.53 LYG, and $263,172 and $228,184 total direct costs, respectively.
- The ICER per QALY gained was $66,064 for ceritinib vs crizotinib and $81,645 for ceritinib vs chemotherapy. The ICER per LY gained over 20 years was $53,207 for ceritinib vs crizotinib, and $$66,441 for ceritinib vs platinum doublet chemotherapy.
- In the first two years following treatment initiation, ceritinib dominated crizotinib by conferring greater health benefits (more QALY) at reduced total costs.

In the sensitivity analysis, results were robust to deterministic and probabilistic sensitivity analyses. The result was most sensitive to ceritinib and crizotinib drug cost per month, drug cost based on treatment until discontinuation, the HR of OS for crizotinib vs ceritinib, and the use of Gompertz function to model ceritinib PFS or OS. They concluded that ceritinib is cost-effective compared to crizotinib and chemotherapy in the treatment of previously untreated ALK-positive metastatic NCSLC in the US. [51]

Li H, et al. (2019) conducted CUA assessing cost effectiveness of ceritinib and alectinib versus crizotinib in first-line ALK-positive advanced NSCLC. The CEA aimed to evaluate the cost effectiveness of ceritinib and alectinib versus crizotinib in the Chinese healthcare setting. They found in the base case analysis, treatment with alectinib, and ceritinib yielded an additional 1.00 and 1.09 QALYs with an incremental

costs of $62,232 and $15,165, resulting in an ICER of $62,231 and $13,905 per QALY, compared with crizotinib, respectively.

Table 20: base-case analysis

Strategy	Cost	QALY	Incremental cost per QALY
Crizotinib	55,180	1.99	NA
Alectinib	118,041	2.99	62,231
Ceritinib 450mg	70,975	3.08	13,905

In the sensitivity analysis, parameters related to drug costs and progression-free survival were the main drivers of the model outcomes. From the probabilistic sensitivity analysis, acceptability curve showed ceritinib and alectinib had a 99.9% and 0% probability of being cost effective, respectively, at a WTP threshold of US$28,410/QALY.

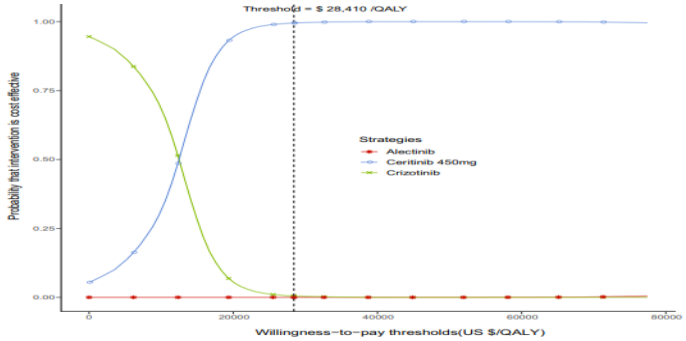


Figure 12: Acceptability curve of ceritinib and alectinib
Source: Li H et al. (2019)

They concluded that compared with crizotinib and alectinib, ceritinib is a cost-effective option for treatment naïve patients with ALK-positive advanced NSCLC. [52]

Liu M, et al. (2019) conducted another CUA assessing cost-effectiveness of ceritinib and alectinib versus crizotinib in the treatment of ALK-positive advanced NSCLC. Cancer Management and Research 2019:11;9195-9202. The CUA aimed to evaluate the cost-effectiveness of crizotinib versus ceritinib or alectinib as first-line-targeted drug therapy for anaplastic lymphoma kinase positive advanced non-small cell lung cancer in China. They found in the base-case analysis, compared with patients who used crizotinib as first-line treatment, patients in the ceritinib and alectinib groups yielded:an additional 1.32 and 3.30 QALYs with an incremental cost of $84,728.20 and $339,114.36. The ICER was: $64,398.83 and $102,675.74 per QALY in the ceritinib and alectinib groups.

Table 21: Cost and outcome from a base case analysis

Strategy	Cost (US$)	QALY	ICER (US$/QALY)
Crizotinib	92,948	1.37	-
Ceritinib	177,676	2.69	64,398
Alectinib	432,063	4.68	102,675
			128,019

When ICER was compared to the threshold ($29,306) the first line crizotinib was the most cost-effective. Compared with Ceritinib, Alectinib was estimated to be more effective (4.68 QALY) and more costly ($432,063) with an ICER of $128,019.42 per QALY (2.69 QALY and $177,676). Results were robust to deterministic and probabilistic sensitivity analyses. The cost of alectinib had the greatest influence on the model. They concluded as a first-line treatment regimen, ceritinib and alectinib can extend the survival time of patients compared with crizotinib, but the medical cost increases accordingly. For the newly diagnosed advanced NSCLC patients and prefer the administration of ceritinib or alectinib, ceritinib is more cost-effective. [53]

Carlson JJ, et al. (2018) in another CUA assessing cost-effectiveness of alectinib vs. crizotinib in first-line ALK-positive advanced NSCLC. They used partition survival methods and three health states: progression free, post-progression, and death in the model. The ALEX trial data informed the progression-free and overall survival estimates for alectinib and crizotinib. The PFS, OS and CNS progression was below.

Table 22: Projected clinical outcomes [54]

Parameter	Alectinib	Crizotinib
Median PFS (month)	23.08	11.77
Median CNS progression (month)	16.79	7.13
Average time spent CNS progression free (month)	41.39	9.17
Average OS (years)	5.21	NA
Average time spent progression free (years)	2.71	NA

In the base-case analysis, treatment with alectinib vs crizotinib resulted in a gain of 0.91 life-years, 0.87 QALY, and incremental costs of US$34,151, resulting in an ICER of US$39,312/QALY.

Table 23: ICER for base-case analysis [54]

Strategy	Total Cost (US$)	QALY
Crizotinib	1,007,968	2.64
Alectinib	1,042,119	3.51
Difference	34,151	0.87
ICER (US$/QALY)	-	39,312

From the sensitivity analysis, drug costs and utilities in the progression free health state were the main drivers of the model in the one-way sensitivity analysis. From the probabilistic sensitivity analysis, alectinib had a 64% probability of being cost effective at a WTP threshold of US$100,000/QALY. They concluded alectinib increased time in the progression free state and quality-adjusted life-years vs. crizotinib. The marginal cost increase was reflective of longer treatment durations in the progression-free state. CNS-related costs were considerably lower with alectinib. The results showed that compared with crizotinib, alectinib may be a cost-effective therapy for treatment naive patients with ALK-positive NSCLC, according to commonly used threshold in US (US$100,000 to US$150,000).[54]

Sivignon M, et al. (2020) in another study evaluated cost-effectiveness of alectinib compared to crizotinib for the treatment of first line ALK positive advanced non-small cell lung cancer in France, from the collective payer (National Health Insurance and private health insurance), and patient perspective. This study used a partitioned survival model, with three discrete health states (progression free survival, post-progression survival and death). Cycle length was one week and time horizon was 10 years. Survival probabilities were derived from a phase III RCT comparing alectinib to crizotinib (ALEX) involving patients with ALK positive NSCLC requiring first line treatment. Beyond the length of the trial (18 months), the efficacy of both treatments was considered equivalent. Occurrence of adverse events or brain metastases were considered as intercurrent events. Utilities (and disutilities for intercurrent adverse events) derived from the EQ-5D were applied. All costs were expressed in 2017 Euro. Costs were attributed using standard French national public health tariffs. Monthly acquisition costs were €4993.63 and €4473.07 for alectinib and crizotinib respectively. Sensitivity analysis evaluated uncertainty of the model. They found projected mean overall survival was 4.6 years for alectinib and 4.2 years for crizotinib, while projected mean progression-free survival was 30.3 months for alectinib and 16.1 months for crizotinib. [55]

Table 24a: Clinical outcomes

Outcome	Alectinib	Crizotinib
Mean OS (months)	4.6	4.2
Mean PFS (months)	30.3	16.1

Table 24b: Base Case Analysis

Parameter	Alectinib	Crizotinib
QALY	3.40	2.84
Total cost	€ 246,022	€ 195,486
ICER/LY	€ 115,334/LY	-
ICER/QALY	€ 90,232/QALY	-

The total number of QALY projected was 3.40 for alectinib and 2.84 for crizotinib. The projected total cost of treatment over the lifetime of the model was €246,022 for alectinib and €195,486 for crizotinib. This extra cost was principally attributable to treatment acquisition costs and management before progression. Alectinib was associated with lower costs related to brain metastases and to management post-progression. The incremental cost per life year gained was 115,334 €/year and the ICER was 90,232 €/QALY. Factors that have the most impact on ICER were the acquisition cost of alectinib and crizotinib. In the PSA, alectinib would be cost-effective in 50% of cases at a WTP threshold of €110,000 and in 70% of cases at a WTP threshold of €162,000. They concluded first-line treatment of ALK positive NSCLC with alectinib provides superior clinical outcomes to crizotinib and is cost-effective in the French context. [55]

Guan H, et al. (2019) in another CUA evaluated cost-effectiveness of alectinib for patients with untreated ALK positive NSCLC in China. They assessed the cost-effectiveness of alectinib versus crizotinib as first-line treatments for advanced ALK positive NSCLC patients from the perspective of China's healthcare system. A Markov

model was developed to assess the clinical outcomes and costs of alectinib and crizotinib, which included five health states: progression-free (PF) without central nervous system (CNS) progression, PF with CNS progression, post-progression (PP) without CNS progression, PP with CNS progression and death. The Markov cycle length was one week, and the time horizon was lifetime.

Table 25a:Estimated clinical outcomes of alectinib vs crizotinib

Outcome	Alectinib	Crizotinib
PFS (years)	3.10	1.47
OS (years)	5.69	4.56
Mean time without CNS progression (years)	1.83	0.67

Table 25b: Base case results

Item	Alectinib	Crizotinib	Difference
LY (total)	5.69	4.56	1.13
QALY (total)	3.26	2.23	1.04
Total cost ($)	150,774	95,947	54,827
ICER	-	-	52,869

They found from the base case analysis, alectinib yielded an additional 1.04 QALYs with incremental costs of $54,827, resulting in an ICER of $52,869/QALY. From the sensitivity analysis, the model outcome was sensitive to the drug cost of alectinib. In probabilistic sensitivity analysis, the probabilities of alectinib being cost-effective were 0.4% and 43.7% when the WTP thresholds were $28,109/QALY and $50,000/ QALY, respectively.

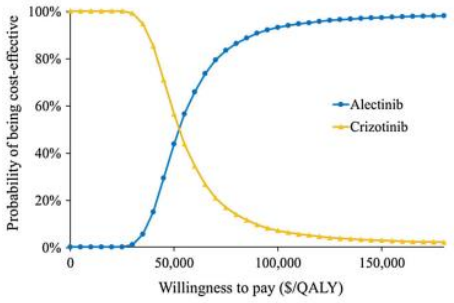


Figure 13: Cost effectiveness acceptability curve
Source: Guan H et al. (2019)

The probability of alectinib being cost effective increase as the drug cost decreases. When the drug cost of alectinib was under $555, probability of alectinib being cost-effective would be higher than 50% at WTP threshold of $28,019. In scenario analysis, the ICER was $56,787/QALY using clinical data from the ALESIA trial. They concluded that alectinib could prolong the mean time of PF and delay the time to CNS progression. However, because of its high drug cost, alectinib was unlikely to be cost-effective for untreated ALK-positive NSCLC patients in China.[56]

Li S, et al. (2021) in another CUA assessed cost-effectiveness of lorlatinib as a first-line therapy for untreated advanced ALK-Positive NSCLC in US. They estimated the cost-effectiveness of lorlatinib as a first-line therapy for patients with advanced ALK-

positive NSCLC. They found in the base case analysis, in which 1 million patients were simulated, the mean cost for lorlatinib and crizotinib as the first-line treatment, LYs, and QALYs were presented below:

Table 26: Base case analysis

Results	Lorlatinib	Crizotinib
Total cost, USD ($)	909,758	616,230
Life-years	6.25	5.45
QALY	4.81	4.09

The total incremental cost was $293,528 which resulted in ICERs of $368,211/LYs and $409,667/QALYs. From the sensitivity analysis, primary drivers of the model were lorlatinib and crizotinib prices, cost of subsequent treatment in the two strategies, and utility of progression free. Probabilistic sensitivity analysis indicated that lorlatinib has 90% cost-effectiveness when compared to crizotinib, when the WTP threshold increased to $448,000/QALY. At a WTP threshold of $200,000/QALY, the probability of lorlatinib being cost-effective is 100% compared to crizotinib when the price of lorlatinib is decreased to 75% of its original price. They concluded in this study, lorlatinib was unlikely to be cost-effective compared with crizotinib for patients with previously untreated advanced ALK+ NSCLC at a WTP threshold of $200,000/QALY.[57]

Nilsson FOL, et al. (2021) in another CUA assessed the cost-effectiveness of lorlatinib versus chemotherapy as a second- or third-line treatment in ALK-positive NSCLC in Sweden. They examined the cost-effectiveness of second- or third-line lorlatinib in Sweden, versus chemotherapy. From the base case analysis, they found:

- For second-line lorlatinib, the average discounted total QALY gain was 1.29 years. The total incremental costs were Swedish krona (SEK) 731,791, resulting in an ICER of SEK566,278 per QALY gained. The non-discounted survival gain amounted to 1.94 years.
- For third-line lorlatinib, the average discounted total QALY gain was 1.25 years. Total incremental costs were SEK754,801, resulting in an ICER of SEK603,934 per QALY gained. Non-discounted survival gain was 1.88 years.

In the sensitivity analysis, the probability of lorlatinib being cost-effective as a second and third-line treatment compared with chemotherapy was almost 100% at a WTP threshold of SEK 1,000,000.They concluded the ICERs ranged from SEK421,000 to SEK384,066 less than the boundary for a cost-effective treatment for a high-severity disease in Sweden (SEK988,000), suggesting second-line or third-line lorlatinib is a cost-effective treatment for ALK-positive NSCLC versus chemotherapy.[58]

Gourzoulidis G, et al.(2022) in another CUA assessed cost-effectiveness of Lorlatinib in patients previously treated with ALK inhibitors for NSCLC in Greece. They assessed the cost-effectiveness of lorlatinib vs pemetrexed with platinum combination of carboplatin or cisplatin (P-ChT) in Greece. They found from the base-case analysis:

- The estimated total costs of lorlatinib and P-ChT over a lifetime horizon were EUR81,754 and EUR12,343, respectively.
- Lorlatinib was more effective than P-ChT with 2.4 and 1.5 more LYs and QALYs gained, respectively.

- The generated ICERs of lorlatinib compared with P-ChT were EUR28,613 per LY gained and EUR46,102 per QALY gained.

The probability of lorlatinib being cost-effective was higher than 75% compared to P-ChT at a WTP of EUR54,000 (three times GDP per capita of Greece). They concluded that the present analysis suggests that lorlatinib may be considered as a cost-effective option compared with P-ChT in Greece for the treatment of patients with advanced, ALK-positive NSCLC whose disease has progressed after at least one second-generation ALK tyrosine kinase inhibitor. In addition, this option addresses a significant unmet medical need.[59]

5.2.7 Organizational

Several biomarkers have emerged as predictive or prognostic biomarkers for NSCLC. A predictive biomarker is indicative of therapeutic efficacy, while prognostic biomarker is indicative of patient survival independent of treatment received. The NSCLC NCCN panel recommends testing for certain biomarkers in all appropriate patients with metastatic NSCLC to assess whether patients are eligible for targeted therapies or immunotherapies. Predictive biomarkers include ALK fusion oncogene, ROS1 gene fusion, sensitizing EGFR gene mutation, BRAF V600E point mutation, NTRK gene fusion and PD-L1 expression.[60]

Molecular testing is used to test for genomic variants associated with oncogenic driver for which targeted therapy is available, these genomic variants (also known as molecular biomarkers) include gene mutation and fusion. Broad molecular profiling system may be used to simultaneously test for multiple biomarkers.[60]

Testing for ALK gene fusion and EGFR gene mutation is recommended in the NSCLC algorithm for patients with metastatic non-squamous NSCLC or NSCLC not otherwise specified. Although rare, patients with ALK fusion or EGFR mutation can have mixed squamous cell histology. Therefore, testing for ALK fusion and EGFR mutation can be considered in patients with metastatic squamous cell carcinoma if they are never smokers, small biopsy specimen was used for testing, or mixed histology was reported. Testing for EGFR mutation and ALK fusion is recommended in mixed squamous cell lung specimen that contain adenocarcinoma component, or in samples in which adenocarcinoma component cannot be excluded.[60]

For patients with metastatic non-squamous NSCLC, the NCCN panel recommended that a minimum of the following biomarkers should be tested; EGFR mutation, ALK fusion, BRAF mutation, ROS1 fusion, and PD-L1 expression level. Biomarker testing should be done at properly accredited laboratories (minimum of Clinical Laboratory Improvement Amendment, (CLIA) accreditation).

Next generation sequencing (NGS) is a type of broad molecular profiling system that can detect panel of mutations and gene fusions if the NGS platform has been designed and validated to detect these genetic variants. It is important to recognize that NGS requires quality control as much as other diagnostic technique. Other mutation screening assays are available for detecting multiple biomarkers simultaneously such as Sequenom's MassARRAY system and SNaPshot Multiplex

System which can detect more than 50-point mutations. However, this multiplex polymerase chain reaction (PCR) system do not typically detect gene fusion. ALK and ROS1 gene fusion can be detected using fluorescence in situ hybridization (FISH), NGS and other method. To minimize tissue use and potential wastage, the NCCN panel recommends that broad molecular profiling be done as part of biomarker testing using a validated test that assess a minimum of the following; EGFR mutation, BRAF mutation, ALK fusion and ROS1 fusion. Both FDA and laboratory-developed test platforms are available that address the need to evaluate these and other analytes. The National Cancer Care Network (NCCN) NSCLC panel recommended testing for ALK fusion in patients with metastatic non-squamous NSCLC based on data showing the efficacy of alectinib, brigatinib, ceritinib and crizotinib for ALK fusion and on the FDA approvals. A molecular diagnostic FISH test has been approved by USFDA for detecting ALK fusion. Rapid pre-screening with IHC to assess for ALK fusion can be done. An IHC assay has also been approved by USFDA. NGS can also be used to assess whether ALK fusions are present, if the platform has been appropriately designed and validated to detect ALK fusions.[60]

According to the NCCN 2020 guideline, alectinib is recommended as 'preferred' first line therapy for patients with ALK rearranged metastatic NSCLC. For the 2020 update, the NCCN panel preference stratified first line therapy with brigatinib, ceritinib or crizotinib for patients with ALK rearranged positive metastatic NSCLC. Brigatinib and ceritinib are 'other recommended options', while crizotinib is useful in certain circumstances. [60]

The NCCN guideline highlighted that alectinib is the preferred first line therapy option (category 1, preferred) if ALK rearrangement is discovered before giving first line systemic therapy (for example pembrolizumab plus chemotherapy), and is a category 2A option (preferred option) if ALK rearrangement is discovered during first line systemic therapy.

For ceritinib, the NCCN panel recommended ceritinib as the first line therapy option for patients with ALK positive NSCLC. Ceritinib is an option (category 1, other recommended option) if ALK rearrangement is discovered before giving first line systemic therapy (eg chemotherapy), and is a category 2A option if ALK rearrangement is discovered during first line systemic therapy.

While for lorlatinib, the NCCN panel recommended lorlatinib as a subsequent therapy option for patients who have progressed after treatment with ALK inhibitors, on either alectinib, brigatinib or ceritinib. Lorlatinib is also a subsequent therapy option for patients with ALK positive NSCLC after progression on crizotinib, followed by progression on either alectinib, brigatinib or ceritinib.[60]

Preferred intervention is intervention that are based on superior efficacy, safety and when appropriate affordability; while 'other recommended intervention' is intervention that may be somewhat less efficacious, more toxic or based on less mature data or significantly less affordable for similar outcome, according to the NCCN categories of preference. [60]

Meanwhile, according to the American Society of Clinical Oncology (ASCO) living guideline for patients with an ALK rearrangement with a performance status (PS) of 0 to 2, and previously untreated NSCLC, clinicians should offer alectinib or brigatinib or lorlatinib. For patients with an ALK rearrangement with a PS of 0 to 2, and previously untreated NSCLC, if alectinib, brigatinib, or lorlatinib are not available; clinicians should offer ceritinib or crizotinib.[61]

According to the earlier ASCO guideline, all patients with non-squamous NSCLC should have the results of testing for potentially targetable mutations (alterations) before implementing therapy for advanced lung cancer, regardless of smoking status recommendations, when possible, following other existing high-quality testing guidelines. Most patients should receive targeted therapy for these alterations; targeted therapies against *ROS*-1 fusions, *BRAF* V600e mutations, *RET* fusions, *MET* exon 14 skipping mutations, and *NTRK* fusions, ALK fusions should be offered to patients, either as initial or second-line therapy when not given in the first-line setting. Alectinib or brigatinib is the optimal first-line treatment for patients with ALK fusions. [62]

The NICE single technology appraisal on ceritinib for untreated advanced ALK positive NSCLC recommended ceritinib within its marketing authorisation, as an option for untreated ALK positive advanced NSCLC in adults, if the company provides it with discount agreed in the patient access scheme. [63]

NICE has previously assessed crizotinib for previously treated ALK positive advanced NSCLC patients. It was not approved but was made available through the cancer drug fund. Another submission subsequently was for different population, patients with previously untreated ALK positive advanced NSCLC. The NICE recommended crizotinib as an option for untreated ALK positive advanced NSCLC in adults once a patient access scheme was agreed.[64]

The Programme in Evidence-Based care (PEBC), Ontario guideline recommended crizotinib as the first line treatment and chemotherapy or ceritinib as the second line treatment among patients with confirmed ALK positive NSCLC. However, at the time of publication of this guideline, alectinib was not approved or available in the market, and trials evaluating ceritinib in patients who were ALK naïve had not been published. [65]

EunetHTA in 2018 conducted HTA on alectinib as monotherapy for ALK positive NSCLC patients. They found from the direct comparison, alectinib demonstrated a substantial increase in PFS, significant longer time to CNS progression compared to crizotinib. The OS data was immature and therefore precluded firm conclusion. Patients receiving alectinib had clinically meaningful HRQoL for a longer duration compared with crizotinib. However, as only one patient was interviewed, no general conclusion can be drawn. The SAE and AE leading to treatment discontinuation occurred at similar frequencies for both alectinib and crizotinib. Alectinib tend to have more favourable safety profile compared with crizotinib. Lower frequency of treatment interruption and dose reduction following alectinib was observed. While conclusion on relative safety compared with ceritinib should be made with caution, both the NMA and

the comparison of the established adverse events profiles indicate an overall superior safety profile of alectinib. [66]

Canada Agency for Drugs and Technologies in Health (CADTH) (2018) in their review found alectinib and ceritinib were more efficacious compared to crizotinib in both first line and second line treatment settings. Alectinib appeared to have a superior efficacy and safety profile followed by ceritinib and crizotinib based on indirect evidence, irrespective of treatment history. However, head to head trials comparing second or newer generation ALK inhibitors are lacking or underway, presenting a challenge in creating a treatment sequence or algorithm based on current evidence. [67]

According to the Agency for Care Effectiveness (ACE) Singapore, for patients with newly diagnosed NSCLC, alectinib, brigatinib, ceritinib and lorlatinib are likely to be more effective than crizotinib in extending the length of time they can live without their cancer getting worse. If the cancer continues to grow while a patient is taking an ALK inhibitor; alectinib, brigatinib, ceritinib and lorlatinib are effective treatment options. Alectinib, brigatinib, ceritinib and lorlatinib were recommended for government funding because they are effective and provide the best value for money for treating ALK mutation-positive advanced NSCLC. Crizotinib was not recommended for funding because its benefits do not justify its cost at the price offered by the company.[68]

ACE recommended ceritinib 150 mg capsules be listed in the Singapore Drug List (SDL), and brigatinib 30 mg, 90 mg and 180 mg tablets be listed in Medication Assistance Fund (MAF) for treating advanced ALK mutation-positive NSCLC (not restricted to specific line of treatment), in view of the current therapeutic gap in the MOH List of Subsidised Drugs, and acceptable clinical effectiveness and cost effectiveness at the prices proposed by the manufacturers. Lorlatinib is indicated for the treatment of patients with locally advanced or metastatic ALK mutation positive NSCLC whose disease has progressed after an ALK inhibitor other than crizotinib, and eligible for MediShield Life claim. Ceritinib, alectinib and brigatinib are recommended for the treatment of locally advanced or metastatic ALK mutation-positive NSCLC and eligible for MediShield Life claim.[69]

5.2.7 Social, ethical and legal

One evidence retrieved on social issue (treatment preference) related to ALK inhibitor in the treatment of patients with advanced ALK positive NSCLC. No evidence retrieved on ethical and legal issues related to ALK inhibitor in the treatment of patients with advanced ALK positive NSCLC.

Lin HM et al. (2021) evaluated real-world patient preferences, experiences and outcomes (health-related quality of life [HRQoL]) from patients with ALK positive NSCLC utilizing the ALKConnect Patient Insight Network. The ALKConnect Patient Insight Network is a patient-focused registry and prospective patient research platform from which cross-sectional real-world data were collected from patients living with ALK positive NSCLC. Study population were ALK positive NSCLC patients enrolled in an online survey over a two-year period between February 2017 and January 2019. Demographics, disease history, status and treatment, patient preferences and HRQoL (MD Anderson Symptom Inventory lung cancer, NDASI-LC module, reported as

symptom severity and interference) were evaluated for 104 US adults with ALK positive NSCLC (median age: 53.0 years, 67.3% female, 40.0% employed). They found in terms of preference, most patients felt that preventing disease progression (92%), treatment response (92%; i.e., shrinking tumor size;), and improved HRQoL (88%) were very important attributes for their current treatment. The mean treatment preference scores (scale 1 to 5; where 1: no influence to 5: most influence) for the treatment attributes were: preventing disease progression 4.723, treatment response 4.657, and improved HRQoL 4.384. In considering a new treatment, a delay in disease progression of an additional one, three and five months was perceived to be meaningful by 41.4%, 57.7% and 68.3% of patients, respectively. The MDASI-LC HRQoL scores were significantly greater for patients with current treatment with ALK TKIs (total symptom severity, p=0.0062, total interference, p=0.0016). The HRQoL was maintained with one or two prior ALK TKIs (not taken concurrently).[70]

6.0 PART B: ECONOMIC EVALUATION

The most common subtype of lung cancer is NSCLC which makes up about 85% of detected lung cancer cases.[17] The common treatment for advanced NSCLC patients without oncogenic driver mutations in Ministry of Health (MOH) facilities is platinum doublet chemotherapy.[16] In addition to chemotherapy, other options for treatment include targeted therapy and immunotherapy. Crizotinib was the first ALK TKI demonstrated to be effective in advanced NSCLC. Next generation ALK TKIs including ceritinib, alectinib and lorlatinib, have since then been developed and have been compared with crizotinib or chemotherapy in RCTs.[17]

For the treatment of NSCLC patients with ALK gene mutation, to date there are five ALK TKIs registered with National Pharmaceutical Regulatory Agency (NPRA) namely crizotinib, ceritinib, alectinib, brigatinib and lorlatinib, but yet to be listed in the MOH Drug Formulary. Hence, as these agents showed promising benefits in maintaining quality of life and improving survival in advanced ALK positive NSCLC patients, their effectiveness and economic implications in the local context should be explored.

The general objective of this economic evaluation was to assess the cost-effectiveness of ALK TKI for advanced ALK positive NSCLC patients. The specific objective was to estimate the incremental cost-effectiveness ratio (ICER) of ALK TKI as the first line treatment in patients with advanced ALK positive NSCLC patients.

6.1 METHODS

6.1.1 Decision analytic and economic modelling

A state transition model (Markov cohort simulation) was developed using Microsoft Excel Workbook 2019 to compare the cost-effectiveness of two different treatment strategies

based on the suggestion from the clinical experts. A hypothetical cohort of patients with ALK gene mutation NSCLC patients were simulated in the following treatment strategies:

1. **First line chemotherapy for the treatment of advanced non-small cell lung cancer.**

   Patients who entered the model will be treated with 4 cycles of chemotherapy and subsequently best supportive care. Patients who progressed will receive 4 cycles of chemotherapy and subsequently best supportive care.

2. **Implementing newer generation ALK TKI (Ceritinib/Alectinib/Lorlatinib) as the first line.**

   Patients who entered the model will be treated with first line of newer generation ALK TKI. Patients who progressed will receive 4 cycles of chemotherapy and subsequently best supportive care.

Model structure

The model structure was constructed with reference to the published studies.[73,74,75] and in consultation with expert committees consisting of multidisciplinary experts namely consultant pulmonologists, consultant clinical oncologists, consultant pathologists, health economists and pharmacists. In general, this Markov model included three health states namely progression free state (PFS), progressed disease state (PD) and dead (D) as the absorption state (Figure 14).

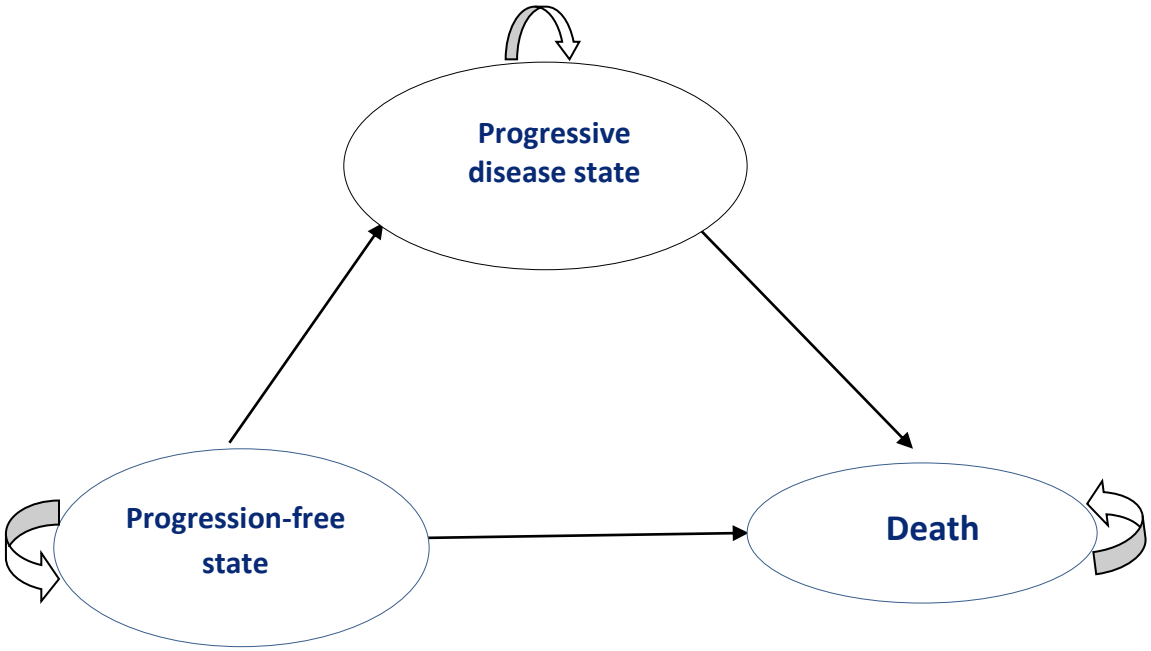


Figure 14: Markov Model

The simulated clinical pathways and model assumptions are as follow:

1. Patients entered the model in the post-diagnosis state after confirmation as detected ALK gene mutation.
2. All health states are mutually exclusive, the patient will not be in other health states while in one particular health states.
3. The health outcome and economic impact related to drug-induced severe adverse events were not included in the model due to no difference in overall adverse events between ALK inhibitors and chemotherapy.[17]
4. Patients in Progressive Disease State will receive best supportive care.
5. The cost and effectiveness of chemotherapy is assumed to be the same regardless of the regime combination of chemotherapy used.

The model decision analyses were conducted from the perspective of Ministry of Health Malaysia and projected to lifetime horizon with one month transition cycle.

Effectiveness Data and Transitional Probabilities

The inputs of transition probabilities were derived from the literatures.[16,73,74] First, the PFS and overall survival (OS) state probability were extracted by the digitizer software from the published Kaplan-Meier curves of PFS and OS from respective literatures. These data were used to fit the survival curves with Weibull survival models using R software to obtain the values of scale lambda (λ) and shape gamma (γ) parameters.[81] The transition probability of disease progression and death at cycte t in the model was estimated as follows: $P(t)=1 – \exp[\lambda(t-1)^{\gamma} - \lambda t^{\gamma}]$.

Table 27: Clinical Input Parameter

Input Parameter	Scale (λ)	Shape (γ)	Reference
Chemo OS	0.012062	1.125845	ASCEND-4 2017[73]
Chemo PFS	0.046197	1.138828	
Ceritinib OS	0.022732	0.923877	
Ceritinib PFS	0.052872	0.919089	
Alectinib OS	0.057001	0.548812	J-ALEX 2017[74]
Alectinib PFS	0.056737	0.637628	
Lorlatinib OS	0.015027	0.999500	Alice T.S et al.2020[75]
Lorlatinib PFS	0.035399	0.835270	
State	**Utility**		
Progression Free	0.653		Nafees 2008[76]
Progressed Disease	0.473		

Cost Input Data

The inpatient lung cancer treatment was calculated from Malaysian DRG Casemix Costing.[77] The chemotherapy outpatient attendances cost was calculated from the direct health-care cost of noncommunicable diseases in Malaysia.[78] The best supportive care cost was

calculated based on published literature.[79] The drug costs used in this analysis were based on feedback from Pharmaceutical Services Program, Ministry of Health.

The regimen for the newer generation ALK TKI was given based on the recommended doses as below:

- Ceritinib: 450mg per day until disease progressed
- Alectinib: 600mg per day until disease progressed
- Lorlatinib: 100mg per day until disease progressed

All cost and utility values are inflated to 2021. The annual discounting rate of 3% was applied.[80]

Sensitivity Analysis

Deterministic sensitivity analysis was performed as one-way sensitivity analysis to assess the model's robustness toward change in parameters. Parameter values were changed with the corresponding maximum and minimum values based on the range. ICER value was measured for each parameter changes. Input parameters tested in sensitivity analyses were:

- Annual discounting rate (0-5%)
- Utility values for progression free state (±10%)
- Cost of inpatient lung cancer treatment (±75%)
- Cost of outpatient attendance (±75%)
- Cost of Best Supportive Care (±75%)
- Cost of Drug (±25% to ±75%)

6.2 RESULTS

6.2.1 Base-case analysis

The base case results of the strategies were presented in the Table 29. The mean total discounted cost and quality adjusted life year (QALY) per patient for ceritinib was MYR206,488.30 and 2.263 respectively, while for alectinib was MYR1,037,522.64 and 5.091, and for lorlatinib was MYR1,217,636.97 and 2.870 respectively.

Table 29: Base-case analysis results

Strategy	Total Cost (MYR)	Total QALY	ICER (MYR)
1 First Line Chemotherapy	65,158.41	1.776	
2 Newer Generation ALK TKI as First Line			
Ceritinib	206,488.30	2.263	290,522.43
Alectinib	1,037,522.64	5.091	293,308.52
Lorlatinib	1,217,636.97	2.870	1,053,681.82

The base case analysis indicated that the deterministic ICER for ceritinib was MYR290,522.43 per QALY gained, while for alectinib was MYR293,308.52 per QALY gained and lorlatinib was MYR1,053,681.82 per QALY gained. All the newer generation ALK TKI were above the cost-effectiveness threshold of one gross domestic product (GDP) per capita per QALY gained for Malaysia.

Sensitivity analysis

One-way sensitivity analysis was performed around the key modal parameters including annual discounting rate, utility values for progression free state, cost of inpatient lung cancer treatment, cost of outpatient attendance, cost of best supportive care and cost of drug. The findings were presented in Table 30, 31 and 32 and plotted as tornado diagram (Figure 15, 16, 17) to illustrate the differences in ICERs obtained given the range of parameter estimates tested.

Table 30: One way sensitivity analysis (Ceritinib)

Parameters	ICER (MYR)	
	Lower Value Input	Higher Value Input
Annual discounting rate	213,454.99	383,450.99
Utility Value (PFS)	392,682.99	230,544.01
Cost of inpatient lung ca treatment	288,721.78	294,875.86
Cost of Outpatient Attendance	242,340.21	338,704.65
Cost of Best Supportive Care	244,181.91	336,862.95
Cost of Ceritinib (±75%)	68,497.65	512,547.21
Cost of Ceritinib (±50%)	142,505.91	438,538.95
Cost of Ceritinib (±25%)	216,514.17	364,530.69

Table 31: One way sensitivity analysis (Alectinib)

Parameters	ICER (MYR)	
	Lower Value Input	Higher Value Input
Annual discounting rate	258,940.41	321,948.52
Utility Value (PFS)	333,047.02	262,042.17
Cost of inpatient lung ca treatment	293,153.45	293,683.43
Cost of Outpatient Attendance	278,476.93	308,140.10
Cost of Best Supportive Care	279,043.85	307,573.18
Cost of Alectinib (±75%)	87,837.43	498,779.61
Cost of Alectinib (±50%)	156,327.79	430,289.24
Cost of Alectinib (±25%)	224,818.15	361,798.88

Table 32: One way sensitivity analysis (Lorlatinib)

Parameters	ICER (MYR)	
	Lower Value Input	Higher Value Input
Annual discounting rate	885,559.24	1,209,172.61
Utility Value (PFS)	1,382,678.65	851,156.29
Cost of inpatient lung ca treatment	1,053,195.70	1,054,857.12
Cost of Outpatient Attendance	1,029,525.66	1,077,837.98
Cost of Best Supportive Care	1,030,449.00	1,076,914.64
Cost of Lorlatinib (±75%)	266,616.05	1,840,747.59
Cost of Lorlatinib (±50%)	528,971.31	1,578,392.23
Cost of Lorlatinib (±25%)	791,326.56	1,316,037.08

By varying the input parameters, the estimated ICER ranged from a lower bound of MYR 68,497.65 per QALY gained to an upper bound of MYR 1,840,747.59 per QALY gained when comparing to conventional chemotherapy. All the ICERs generated were higher than one GDP per capita per QALY gained.

Sensitivity analyses of variables in the model showed that the ICER is sensitive to changes in the annual discounting rate, utility value of progression free state and cost of the newer generation ALK TKI.

By varying the discount rate, all the newer generation ALK TKI shows a lower value of ICER at the 0% discount rate and higher value of ICER at the 5% discount rate.

Reducing the utility value of progression free state will increase the ICER while increasing the utility value of progression free state will decrease the ICER for all the newer generation ALK TKI.

For the cost of the newer generation ALK TKI, reducing the drug cost to 75% for all also showing significant reduction of ICER even though it was still higher than one GDP per capita per QALY gained.

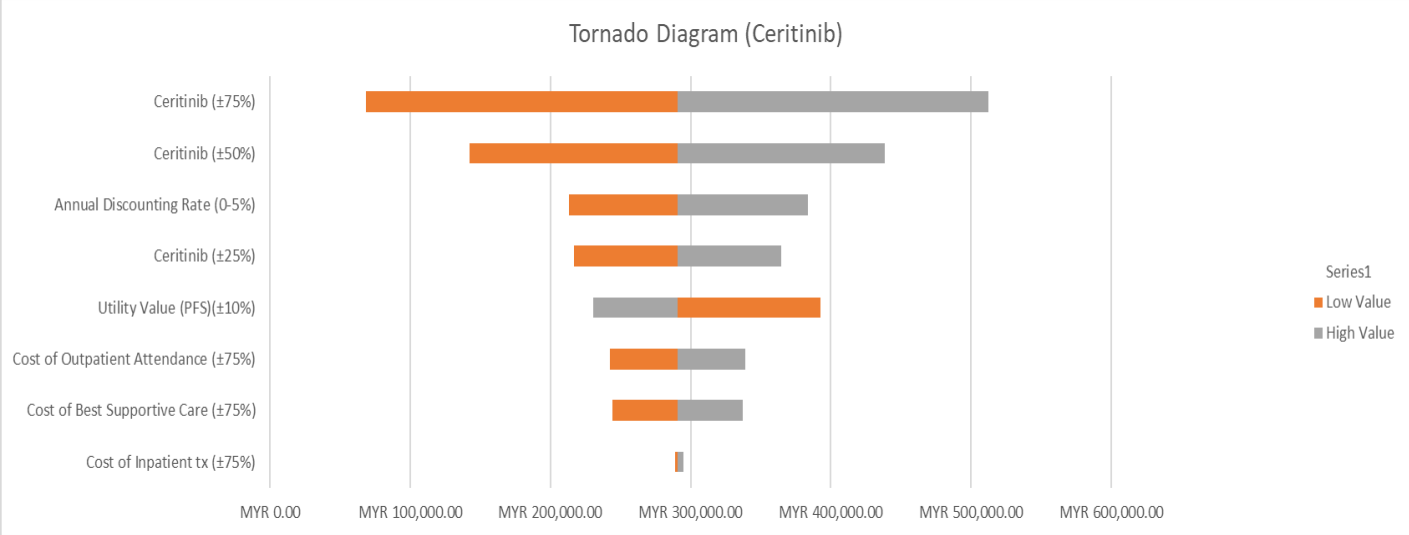


Figure 15: Tornado diagram ceritinib (one way sensitivity analysis)

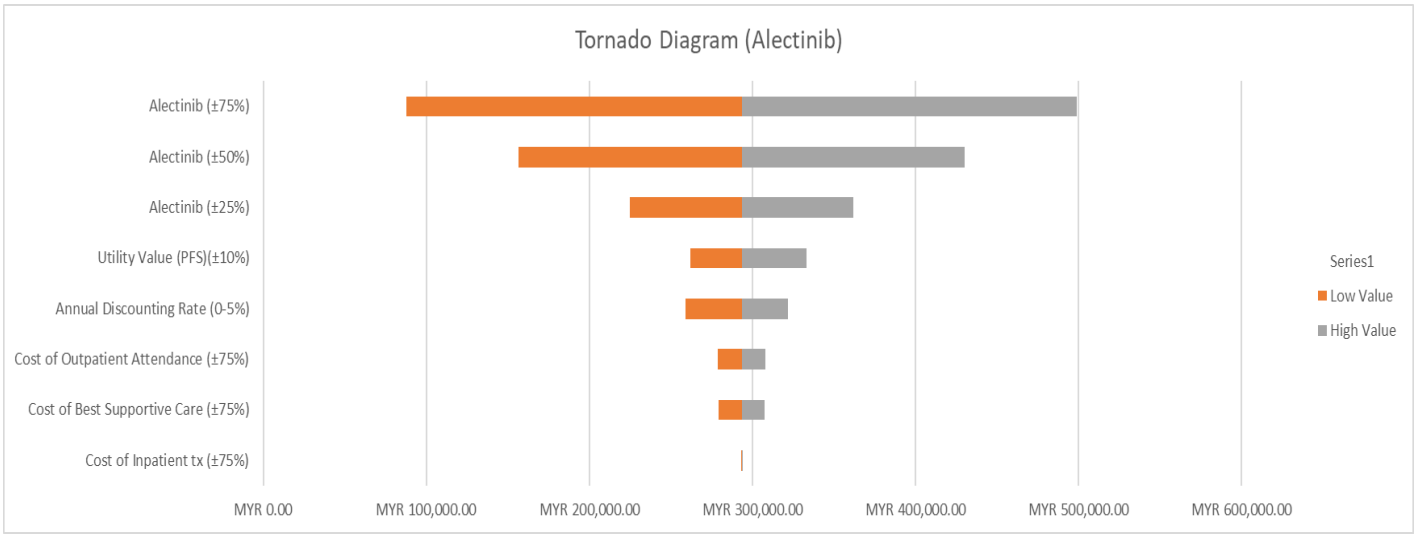


Figure 16: Tornado diagram alectinib (one way sensitivity analysis)

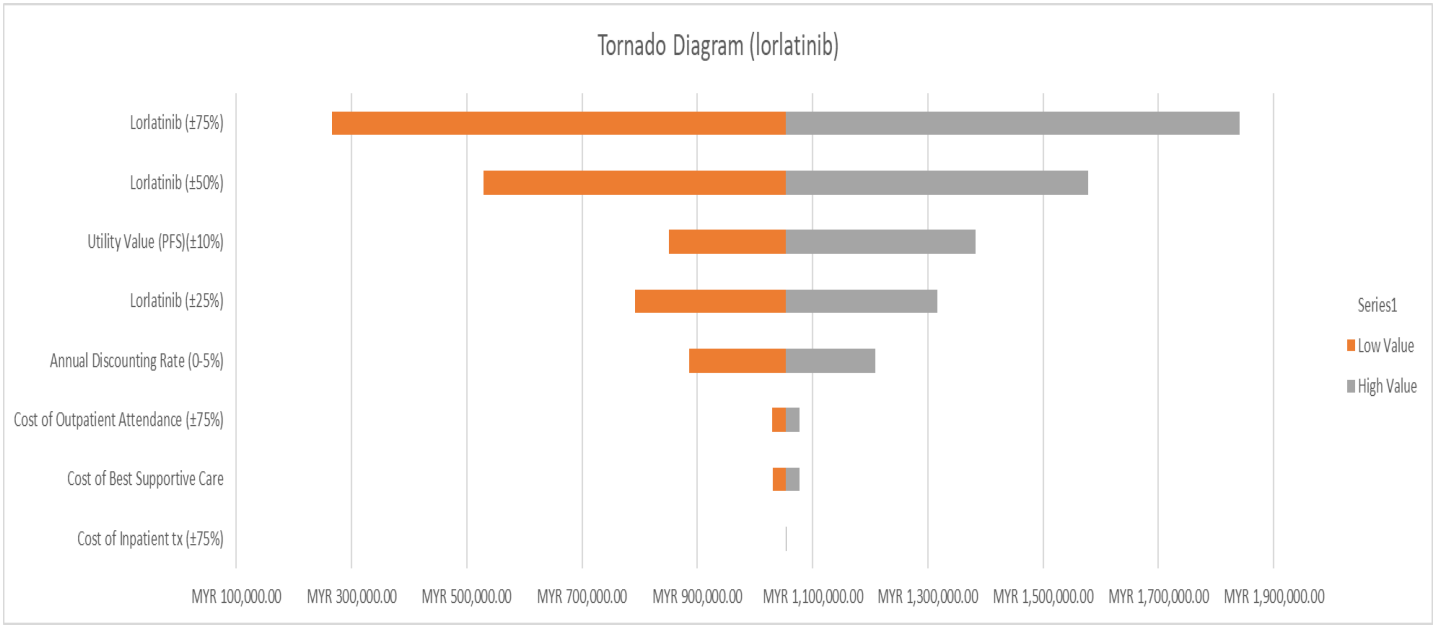


Figure 17: Tornado diagram lorlatinib (one way sensitivity analysis)

6.2.2 Limitation of local economic evaluation

One of the limitations of these analyses is the lack of real-world local data to represent the local scenario. Besides, the model did not include the cost for the genetic tests. This is due to the limitation that in the current public hospitals setting there was no facilities for ALK gene rearrangement test. The cost needed for the setting up genetic laboratory, equipment and reagents for early genetic test might be higher, thus could possibly contributed to the cost for the outcomes to be underestimated.

7.0 DISCUSSION

We obtained finding from 16 studies in the review of effectiveness and safety, while 12 studies in the review of cost-effectiveness, investigating ALK inhibitor as monotherapy for the treatment of advanced ALK positive NSCLC. The included studies (all SR for effectiveness and safety; and all primary cost-effectiveness analysis for cost-effectiveness section) were published in English language between 2016 and 2022 and were conducted in the United States, Canada, Italy, China, Hong Kong and Egypt. The primary studies included in the SR were from multicountries (Japan, South Korea, Thailand, Australia, Bosnia, Brazil, Canada, Chile, China, Costa Rica, Denmark, France, Germany, Greece, Guatemala, Israel, Mexico, New Zealand, Peru, Portugal, Russia, Singapore, Spain, Switzerland, Taiwan, Turkey, Ukraine and UK). The SR included in this review comprised mainly of SR of RCTs, with two were SR of RCT and observational studies, with a range of three to 21 primary studies included in the SR. Overall in total, this review enrolled 31,614 participants with histologically confirmed advanced ALK positive NSCLC adult patients whose ECOG status was 0 to 2 (range of 697 to 5653 participants). Some of the primary studies included in the SR were also reviewed in another SR included in this review. The longest time of follow-up documented in the review was up to 42.4 months. Of the SR assessing effectiveness and safety, 12 evaluated several ALK TKIs compared to chemotherapy or crizotinib, three evaluated alectinib and one evaluated ceritinib. There was variation in the involvement of brain metastasis in the study population, as well as variation in the line of treatment of ALK inhibitors used in the study population, whereby most of the SR included studies that examined ALK inhibitors as the first and second lines, with three SR evaluated its use in the first line setting. Outcomes of this review were OS, PFS, AE, ORR, time to CNS progression, and HRQoL. PFS was available in most of the included studies in the review, unlike the other outcomes.

Evidences supporting ALK inhibitors has evolved, first demonstrating benefit against second line chemotherapy, then crizotinib as upfront therapy, and recently second-generation ALK inhibitors as the first line treatment. [35]

Our review found ALK inhibitors is beneficial in improving PFS, OS, ORR and HRQoL compared to chemotherapy in patients with advanced ALK positive NSCLC. This review also found the next generation ALK inhibitors including ceritinib, alectinib, lorlatinib offered greater clinical benefit with superior PFS and OS compared to crizotinib (as the first line treatment in patients with advanced ALK positive NSCLC). Treatment with ALK inhibitors resulted in large improvement in PFS compared to chemotherapy or crizotinib, which was the primary outcome in most of the included studies. This was the case regardless of the line of treatment and for participants with baseline CNS involvement. ALK inhibitors resulted in increase in OS, compared to chemotherapy regardless of line of treatment or type of ALK inhibitor. The magnitude of benefit, in trials where cross over was allowed was much less than was seen in PFS. A number of participants randomised to chemotherapy later crossed over to receive ALK inhibitor. Only one review reported HRQoL measure, all of which showed an improvement in the time to deterioration composite endpoint (cough, dyspnoea and chest pain) for ALK inhibitors compared to chemotherapy.

Our findings support the use of next generation ALK inhibitor and the findings are in line with international clinical guidelines, as well as review by the EunetHTA and by CADTH on ALK inhibitor in these patients. The findings are in line with other systematic reviews published recently. Chuang et al. (2021) limited their review to first line therapy, evaluated ALK inhibitor using indirect comparison and NMA to rank first line ALK inhibitors. They concluded that all next-generation ALK improved PFS when compared to crizotinib (HR 0.41). Improved PFS was observed in patient with baseline CNS involvement as well. Lorlatinib had the best PFS using SUCRA analysis.[71] Another review by Khan et al. (2019) assessed PFS as the primary outcome in their review. Consistent with this review, they found superiority of ALK inhibitor in PFS, ORR and intracranial response. However, they found no difference in OS following ALK TKI compared to chemotherapy. They highlighted cross-over as a potential confounder in the OS outcome in the review.[72]

It was reported in some of the review that there was no statistically significant OS benefit for ceritinib or crizotinib compared with chemotherapy, and there was significant crossover from the chemotherapy arms to the TKI arms, leading to uncertainty about the true treatment effect of the TKIs. Similarly for alectinib versus crizotinib, it was reported that OS data was immature from both ALEX and ALTA-1 trials, and comparison of OS outcomes was potentially confounded by indirect nature of the comparison, differences in the duration of follow up and differences in practice between trials.[69]

Limitations

We acknowledge some limitations in our review and these should be considered when interpreting the results. Although there was no restriction in language during the search, only full text articles in English published in peer-reviewed journals were included in the review, which may have excluded some relevant articles. We included only SR in the review of clinical effectiveness and CEA in review of cost-effectiveness. By limiting our included studies to SR of RCT, we pursued the highest level of evidence. However in doing so, primary studies addressing other relevant and recent outcome may have been excluded. Another limitation was the methodological quality of the included studies, such as heterogeneity of the SR and risk of bias. Included studies with high risk of bias may affect methodological quality of this review. There was some limitation in the exact line of treatment in the population included in this review, whereby not all the SR included described clearly the line of treatment used whether specific in the first line setting (naïve population) or further or subsequent line setting (second or third line) in pre-treated population. The NMA included in this review consisted of the most comprehensive list of trials. However, the indirect comparison and ranking of treatment were done using pooled data from a mix of patients who were ALK naïve and pre-treated (patients with and without prior exposure to ALK inhibitors). The pairwise meta-analysis for ALK naïve subgroup did not always compare two or more ALK, and pairwise meta-analysis for ALK pre-treated subgroups compared a particular ALK against all ALK as a group. Comparative studies did not always discriminate between ALKinhibitor naive and experienced patients. More RCTs and/or NMAs comparing ALK inhibitor against each other would be helpful, in ALK inhibitor naive as well as in pretreated patients. There was variation in the term or definition used for patient with brain involvement in the included SR, such as brain involvement, measurable and non-measurable brain metastasis, as well as baseline CNS disease. There was no access to individual patient data for analysis, hence we could not examine the influence of individual patient characteristic with the outcomes of this review, such as age, gender or smoking status. The longest patient's follow-up was 42

months in this review, therefore more long-term studies to ascertain that the effectiveness of ALK inhibitor is sustained would be beneficial. Health related quality of life (HRQoL) measures are important outcome given that these treatments are often taken for years until disease progression, hence more studies evaluating HRQoL measures in future would be required.

8.0 CONCLUSION

Based on the above review, there was good level of evidences on ALK TKI to be used in the management of patients with advanced ALK positive NSCLC.

This review showed overall ALK inhibitors appeared beneficial in improving PFS, OS, ORR, intracranial ORR and HRQoL compared to chemotherapy or crizotinib in patients with advanced ALK positive NSCLC.

Next generation ALK inhibitors including ceritinib, alectinib, lorlatinib offered greater clinical benefit with superior PFS and ORR compared to crizotinib (**as the first line treatment** in patients with advanced ALK positive NSCLC). Evidence of next generation ALK inhibitors on OS was inconclusive.

- Alectinib 600mg showed the highest probability (in OS), followed by lorlatinib and ceritinib, over other interventions in all advanced ALK positive NSCLC patients.

- Lorlatinib showed the highest probability (in PFS), followed by alectinib and brigatinib, over other interventions in advanced ALK positive NSCLC patients with brain metastasis.
  Next generation ALK inhibitor namely alectinib and lorlatinib were superior than chemo or crizotinib in improving PFS, with HR for alectinib ranges from 0.12 to 0.41, and HR for lorlatinib ranges from 0.54 to 0.59.

- Alectinib showed the highest probability (in ORR) followed by brigatinib in the advanced ALK positive NSCLC patients (first line setting).
  Next generation ALK inhibitor improved ORR compared with crizo in all advanced ALK positive NSCLC and in patients with BM, [RR of 1.18(95%CI 1.10 to 1.25) to RR 2.45(95% CI 1.7 to 3.54)].

Next generation ALK inhibitor including alectinib, lorlatinib, brigatinib was demonstrated to be superior in OS, PFS, ORR, intracranial ORR, and HRQoL compared with chemo or crizotinib in advanced ALK positive NSCLC in the further line of treatment.

- Alectinib showed the highest probability (in OS) vs chemotherapy or crizotinib in advanced ALK positive NSCLC patients in the further line setting.
  ALK inhibitors improved OS compared to chemo or crizotinib in these patients with HR ranging from 0.66 to 0.84.

- Lorlatinib showed the highest probability (in PFS) followed by alectinib and brigatinib, in both all ALK positive NSCLC patients and patients with BM. ALK inhibitors improved PFS compared with chemo or crizotinib in these patients (HR range 0.34 to 0.45).

- Brigatinib showed the highest probability (in ORR), followed by lorlatinib and alectinib in advanced ALK positive NSCLC patients.
  ALK inhibitor improved **ORR** compared to chemo (RR from 2.43 (95%CI 2.16 to 2.75) to 4.88(95%CI 2.18 to 10.95) from all ALK positive NSCLC patients to patients with BM.

- Lorlatinib showed the highest probability for intracranial response rate (probability of 44%).
  ALK inhibitor improved **intracranial ORR** in both naïve and pre-treated ALK positive NSCLC patients (39.2% and 44.2%, respectively).

- ALK inhibitors resulted in a large increase in the **Health-Related Quality of Life (**HRQoL) measured (HR 0.52, 95% CI 0.44 to 0.60) compared to chemotherapy.

- Cumulative incidence of CNS progression following alectinib
  -10% (95%CI 5 to 16%) : six months
  -16% (95%CI 9 to 24%) : 12 months

Safety
Crizotinib, ceritinib, brigatinib, alectinib and lorlatinib were registered with USFDA, indicated for the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test, and registered with NPRA. ALK inhibitors appeared safe with similar overall AE rates compared with chemotherapy. Risk of grade three or higher AE was not significantly different between ALK inhibitor compared to chemotherapy, or between next generation ALK inhibitor and crizotinib. The most common SAE reported were dyspnoea and pneumonia. Hepatic toxicities were more common following crizotinib and ceritinib, peripheral oedema following crizotinib and alectinib, and visual disorders was only reported with crizotinib.

Cost-effectiveness
Cost-utility analysis conducted in various countries from payer and provider perspective demonstrated that the ICER varies from $13,343/QALY to $230,661/QALY comparing ceritinib versus chemotherapy or crizotinib. Comparing alectinib versus crizotinib, the ICER ranges from $39,312/QALY to €90,232/QALY; and comparing lorlatinib versus crizotinib or chemotheraphy the ICER ranges from €46,102/QALY to $409,667/QALY. Ceritinib offered a cost-effective option compared to crizotinib or chemotherapy in Hong Kong and Canada. Alectinib offered a cost-effective option in the US as the first line treatment in patients with advanced ALK positive NSCLC.

Organizational
For patients with metastatic non-squamous NSCLC, the NCCN panel recommends that a minimum of the following biomarkers should be tested; EGFR mutation, ALK fusion, BRAF mutation, ROS1 fusion, and PD-L1 expression level. Biomarker testing should be done at properly accredited laboratories (minimum of Clinical Laboratory Improvement Amendment, (CLIA) accreditation).

The American Society of Clinical Oncology (ASCO) living guideline (2022) recommendation for patients with ALK rearrangement, with a performance status (PS) of 0-2, and previously untreated NSCLC, was for clinicians to offer them with alectinib or brigatinib or lorlatinib. For these patients, if alectinib, brigatinib, or lorlatinib are not available, then they should be offered ceritinib or crizotinib.

According to the National Cancer Care Network (NCCN) 2020 guideline, Alectinib is recommended as the 'preferred' first line therapy for patients with ALK rearranged metastatic NSCLC. The NCCN panel preference stratified first line therapy with brigatinib, ceritinib or crizotinib for patients with ALK rearranged positive metastatic NSCLC. Brigatinib and ceritinib are 'other recommended options', while crizotinib is useful in certain circumstances. They recommended lorlatinib as a subsequent therapy option for patients who have progressed after treatment with ALK inhibitors, on either alectinib, brigatinib or ceritinib. Lorlatinib is also subsequent therapy option for patients with ALK positive NSCLC after progression on crizotinib, followed by progression on either alectinib, brigatinib or ceritinib.

The NICE single technology appraisal (2019) recommended ceritinib as an option for untreated ALK positive advanced NSCLC in adults, if the company provides it with discount agreed in the patient access scheme. NICE recommended crizotinib as an option for untreated ALK positive advanced NSCLC in adults once a patient access scheme was agreed (2017).

Social, ethical, legal

In terms of preference, most patients felt that preventing disease progression (92%), treatment response, and improved HRQoL were very important attributes for their current treatment. In considering a new treatment, a delay in disease progression of an additional one, three and five months was perceived to be meaningful by 41.4%, 57.7% and 68.3% of patients.

Local economic evaluation

From the economic evaluation, ICER for the newer generation ALK TKI; ceritinib, alectinib and lorlatinib were all higher than cost-effectiveness threshold of one GDP per capita per QALY gained for Malaysia. Among these three ALK TKIs, ceritinib and alectinib were found to be more cost-effective compared to lorlatinib. The one-way sensitivity analysis indicated that the annual discounting rate, progression free state utility values and cost of the newer generation ALK TKI have shown to be the sensitive parameters for ICER and may be a key determinant before considering the first line treatment for advanced non-small cell lung cancer for the ALK gene mutation patients. Reduction of drug price demonstrated a significant reduction of ICER.

9.0 RECOMMENDATION

Based on the above review, ALK inhibitors (ceritinib, alectinib, lorlatinib) offer greater clinical benefit and acceptable safety profile compared to chemotherapy or crizotinib in patients with advanced ALK positive NSCLC.

In view of the current therapeutic gap, ceritinib may be used as a standard treatment option for patients with advanced and metastatic ALK positive NSCLC. Alectinib should be considered in advanced ALK positive NSCLC patients who have progressed after treatment with ALK inhibitors other than crizotinib, or patients intolerant to ceritinib or crizotinib. To meet the treatment needs, competitive price or appropriate drug assistance policies should be provided.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I	Evidence obtained from at least one properly designed randomised controlled trial.
II-I	Evidence obtained from well-designed controlled trials without randomisation.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)

APPENDIX 2: HEALTH TECHNOLOGY ASSESSMENT PROTOCOL

ANAPLASTIC LYMPHOMA KINASE (ALK) TYROSINE KINASE INHIBITOR FOR ALK POSITIVE NON-SMALL CELL LUNG CANCER

1.0 BACKGROUND INFORMATION:

1.1 INTRODUCTION

Worldwide, lung cancer is the leading cause of cancer-related death. In 2020, there were 2.2 million incident cases of lung cancer (11.7%) and 1.8 million deaths (18.0%) globally. The highest lung cancer incidence (59.6%) and mortality (61.9%) were reported in Asia. [1] In Malaysia, lung cancer is the third most common cancer, accounting for 9.8% of all cancer cases.[2] In the 25-59 age group it is the second most common cancer (13.4%) and the incidence further increases in the 60-74-year-old group (17.9%).[2] Although majority of cases were detected in current or ex-smokers, increasingly patients with minimal or no smoking history were being diagnosed.[3]

Nearly 90% of lung cancer cases in Malaysia are diagnosed at an advanced stage (stage III or stage IV).[2] The 5-year observed survival rate is only 9.0% (95%CI 8.4 to 9.7).[4] A local study of lung cancer survival at a tertiary hospital reported an overall median survival of only 18 weeks for patients presented with either stage III or stage IV disease without definitive treatment. Approximately 94% of patients with advanced stage III or stage IV disease were diagnosed with non-small cell lung cancer (NSCLC).[5]

The NSCLC accounted for nearly 85% of all lung carcinoma cases with three major pathologic subtypes; adenocarcinoma, squamous cell carcinoma and large cell carcinoma.[6] Adenocarcinoma is the most common histological subtype of lung carcinomas diagnosed within the Malaysian population.[7] Anaplastic Lymphoma Kinase (ALK) positive NSCLC represents approximately 4% to 5% of all NSCLC patients in both Caucasian and Asian populations.[8] This still represents potentially 40,000 new cases worldwide each year, given the worldwide prevalence of NSCLC.[9] Patients with ALK rearrangements have distinct clinicopathologic features such as adenocarcinoma with signet ring or acinar histology, is typically seen in those with relatively young age, with a never or light (<10 pack years) smoking history.[10] ALK positive NSCLC patients have a high risk of developing brain metastases, as observed in at least 20% of cases at the time of the initial diagnosis.[11] These patients harbour a genetic rearrangement in the ALK gene, resulting in a novel fusion oncogene *EML4-ALK* that leads to constitutive expression of intracellular signaling pathway that promote tumour growth and survival.[12]

Until recently, the standard first-line treatments for patients with NSCLC with no driver mutations [EGFR, ALK or receptor tyrosine kinase (ROS1) genomic aberrations] was platinum doublet chemotherapy, achieving modest improvement, with median progression-free survival (PFS) of five to six months, and median overall survival (OS) of 11 months (squamous histology) to 17 months (non-squamous histology).[13,14]

The management of advanced NSCLC has transformed due to improvement in the understanding of molecular drivers of carcinogenesis. The discovery of oncogenes, such as the EGFR, ALK and the others along with the development of medications specifically targeting these mutations have led to the ability to personalize therapy.[15] For this subgroup of advanced NSCLC patients, the treatment paradigm has evolved from non-specific curative approaches, to the use of therapy targeting particular actionable genetic mutations.[16] Patients with ALK rearrangement have been identified as subgroup of lung cancer patients to gain survival benefit from targeted therapy.[17] International guidelines recommended testing for ALK mutation in all non-squamous NSCLC.[18] Detecting ALK gene rearrangement in newly diagnosed NSCLC is essential as the presence of this oncogene influence treatment decision. The ALK gene rearrangement can be detected in clinical samples using several techniques, primarily fluorescence in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR), immunohistochemistry (IHC), next-generation sequencing (NGS), liquid biopsy, and new potential biomarkers such as circulating tumor cells (CTCs), cell-free DNA, and exosomes are being investigated.[19]

1.2 TECHNOLOGY DESCRIPTION

The *ALK* gene is located on the short arm of chromosome 2 (2p23), belongs to the insulin receptor superfamily, and encodes for the ALK protein. ALK is a transmembrane tyrosine kinase receptor, which is physiologically expressed in the nervous system during embryogenesis. ALK was originally identified in anaplastic large-cell lymphoma hence the name anaplastic lymphoma kinase. Subsequently, ALK-rearrangement (ALK-R) was identified in the pathogenesis of several cancers, including inflammatory myofibroblastic tumors, diffuse large B-cell lymphoma, esophageal squamous cell and colorectal carcinomas. In 2007, ALK gene arrangement was discovered in NSCLC. There are three types of *ALK* gene mutations: rearrangement (ALK-R), amplification (ALK-A), and point mutation. Most mutations of the *ALK* gene are in the form of a translocation with another partner gene leading to a fusion oncogene. This fusion gene then becomes overly expressed in cancers. ALK rearrangements create an oncogenic ALK tyrosine kinase that activates many downstream signaling pathways resulting in increased cell proliferation and survival. More than 19 different ALK fusion partners have been discovered in NSCLC, including EML4, KIF5B, KLC1, and TPR.[20] The most common alteration of ALK is the fusion of ALK gene with the echinoderm microtubule associated protein like -4 (EML4) gene.[21] This gene alteration was resulted from interchromosomal inversion within the short arm of chromosome 2 joining the exons 1-13 of the EML4 gene, to exons 20-29 of ALK gene.[22] NSCLC with positive ALK-EML4 gene fusion is highly sensitive to ALK inhibition by molecules designed to target tyrosine kinase. [21]

The therapeutic landscape of ALK positive NSCLC has led to the introduction of three generations of ALK TKI involving different highly potent molecules.[23] Table 1 summarizes the sequence of approval for the available ALK TKI.

Crizotinib is the first generation TKI with recommended dose of 250 mg twice daily in a 28-day cycle until disease progression or no longer tolerated by the patient. It is a multi-targeted TKI, was first discovered to inhibit the c-MET pathway but has also proved to inhibit the ALK and ROS1 gene.[24] Crizotinib was the first TKI approved in 2011 by the USFDA for metastatic

NSCLC patients with ALK mutation, however almost a third of the patients had developed primary or secondary resistance within one to two years.[25]

Ceritinib is a second-generation ALK TKI which is 20 times as potent as crizotinib, with a therapeutic dose of 450 mg orally once daily, and is the initial second-generation ALK TKI approved to overcome resistance to crizotinib. In 2014, ceritinib was indicated to ALK-positive patients with disease progression on or intolerance to crizotinib, subsequently indicated as first-line therapy in 2017. Ceritinib inhibits the autophosphorylation of ALK, and the molecular targets include IGF-1 R, InsR, and ROS1. Ceritinib inhibits the most common ALK mutations, such as L1196 M, G1269A, I1171T, and S1206Y, which determine resistance to crizotinib. In patients who progressed during ceritinib treatment, secondary mutations were detected such as G1202R, F1174 C/L, C1156Y, G1202del, and L1196M. The F1174L mutation can be resistant to ceritinib but sensitive to alectinib.[26]

Alectinib is a highly potent second-generation ALK that also has RET (Rearranged during Transfection) gene activity inhibitor, with recommended twice-daily dose of 600 mg.[27] Alectinib is indicated for NSCLC patients with ALK rearrangement who have benefited previously from crizotinib, approved in 2015 and subsequently indicated as first-line therapy in 2017. Due to its chemical structure, it is efficient for patients with crizotinib-resistant ALK mutations.[28]

Brigatinib is a highly potent selective second generation ALK inhibitor. It was approved by USFDA as a first line option for patients with ALK positive NSCLC in 2020, with recommended dose of 90mg orally once daily for first seven days then increase to 180mg orally once daily, until disease progression or unacceptable toxicity.[29]

In order to overtake acquired resistance, prolong the control of the disease, and manage CNS disease, several highly potent next-generation ALK TKIs have been developed such as lorlatinib and ensartinib.[30] Lorlatinib is a third-generation ALK- and ROS1-inhibitor, a selective, brain penetrating ALK TKI, designed to target mutations which drive resistance to crizotinib and next-generation TKIs. Recommended dose is 100 mg once daily, approved in 2018 by the USFDA as the first-line therapy for metastatic NSCLC patients and ALK rearrangement with progressive disease on crizotinib and other ALK inhibitors.[31] Lorlatinib is a macrocyclic TKI, smaller and more compact compared to the first and second generation which is an acyclic TKI. [24]

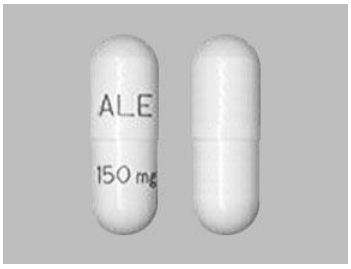
Ensartinib is a novel second-generation ALK inhibitor created to improve the activity on CNS metastases. This small molecule displayed activity against MET, Axl, ABL, EPHA2, LTK, ROS1, and SLK genes. Entrectinib is a potent, selective, oral inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK, with the ability to cross the blood - brain barrier and possess a strong intracranial activity.[24]

Table 1: ALK TKI for treatment of NSCLC approval status

Drugs	FDA Indication	Date of USFDA Approval	MOH Registration Status	MOH Formulary
Crizotinib	• Patients with late-stage (locally advanced or metastatic), NSCLC who express the abnormal ALK gene • Patients with metastatic NSCLC whose tumors are ALK or ROS1-positive as detected by an FDA-approved test.	2011 11 March 2016	Yes Xalkori 200mg & 250mg Capsules (Pfizer)	Not available (NA)
Ceritinib	• For the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test	26 May 2017	Yes Zykadia 150mg Hard Capsules (Novartis)	NA
Alectinib	• For the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.	6 November 2017	Yes Alecensa Hard Capsules 150mg (Roche)	NA
Brigatinib	• For the treatment of patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.	22 May 2020	Yes Alunbrig (Brigatinib) 30mg, 90mg & 180mg Film-Coated Tablet (Takeda Pharmaceutical)	NA
Lorlatinib	• For the treatment of adult patients with metastatic NSCLC whose tumors are ALK-positive as detected by an FDA-approved test.	3 March 2021	Yes Lorviqua 25 mg & 100 Film-Coated Tablets (Pfizer)	NA
Entrectinib	• Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive. • Adult and pediatric patients 12 years of age and older with solid tumors that: ○ have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, ○ are metastatic or where surgical resection is likely to result in severe morbidity, and ○ have progressed following treatment or have no satisfactory alternative therapy.	15 August 2019	NA	NA

a)Crizotinib (xalkori)

b)Ceritinib (zykadia)



c)Alectinib (alecensa) d)Lorlatinib (lorbrena)

Figure 1: Physical appearance of several ALK TKI inhibitors

1.3 Targeted therapy ALK TKI for ALK positive advanced NSCLC in Malaysia

Majority of lung cancer patients in Malaysia are diagnosed with locally advanced or metastatic disease, hence preclude curative surgical resection.[2] Several ALK-TKI were registered with National Pharmaceutical Regulatory Agency (NPRA), however they are not available in the MOH formulary. Targeted therapies were mostly hard to afford via out-of-pocket by patients without private health insurance. Most patients who cannot afford ALK TKI opt for chemotherapy. As of now, entrecnib and ensartinib are still not registered in Malaysia. Table 2 highlight their approval and availability in public hospitals.[32] In 2019, a consensus statement on Molecular Testing for Advanced NSCLC patients localized to Malaysian setting was published. According to the document, 'must-test' biomarkers which are standard-of-care for all advanced lung cancer patients with an adenocarcinoma component who are being considered for an approved targeted therapy include testing for EGFR mutation, ALK rearrangement, ROS1 rearrangement and BRAF mutation.[16] The EGFR, ALK and PD-L1 testing are being reimbursed while the others are not.[32] However, the high cost of molecular testing and systemic therapy limit the availability of treatment options for many Malaysian population.[32] Besides that, as there have been many new ALK TKI approved for ALK positive NSCLC, the review is timely to address the increasing need to provide targeted therapy with better efficacy and lower toxicity in advanced ALK positive NSCLC patients in the country. Therefore, this assessment will evaluate whether it would be effective, safe and cost-effective to use targeted therapy, ALK TKI in the management of ALK positive advanced NSCLC patients in Malaysia as requested by a Clinical Oncologist from Kuala Lumpur Hospital.

Table 2: ALK TKI registration and reimbursement status in Malaysia

Drug	Approved in first line	Approved in second line	Available for free (public hospitals)	Reimbursement (private insurance)
Crizotinib	Yes	Yes	No	Yes
Ceritinib	Yes	Yes	No	Yes
Alectinib	Yes	Yes	No	Yes

2.0 POLICY QUESTION:

Should targeted therapy (ALK tyrosine kinase inhibitor) be used as a standard treatment option for patients with advanced and metastatic ALK positive NSCLC in the Ministry of Health hospitals?

3.0 OBJECTIVES:

3.1 The following are the objectives of this review:

i. To assess the comparative effectiveness and safety of ALK tyrosine kinase inhibitors given as monotheraphy to treat patients with advanced and metastatic ALK positive NSCLC
ii. To determine the economic, organizational, social, ethical and legal implications of ALK tyrosine kinase inhibitors given as monotheraphy to treat patients with advanced and metastatic ALK positive NSCLC

3.1 The following are the research questions of this review:

i. How effective and safe are the ALK TKIs given as monotherapy in the treatment of patients with advanced and metastatic ALK positive NSCLC?
ii. How cost-effective are the ALK TKIs given as monotherapy in the treatment of patients with advanced and metastatic ALK positive NSCLC?
iii. What are the organizational, social, ethical and legal implications of ALK TKIs in the treatment of patients with advanced and metastatic ALK positive NSCLC?

4.0 METHODS

4.1 Search Strategy

4.1.1 Electronic databases will be searched for published literatures pertaining to ALK TKI for ALK positive NSCLC.Databases are as follows; MEDLINE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), Horizon Scanning, INAHTA Database, HTA database and FDA database.
4.1.2 Additional literatures will be identified from the references of the related articles.
4.1.3 General search engine will be used to get additional web-based information if there is no retrievable evidence from the scientific databases.
4.1.4 There will be no limitation applied in the search such as year and language.
4.1.5 The search strategy will be included in the appendix.

4.2 Inclusion and exclusion criteria

4.2.1 Inclusion criteria

Population Problems	Patients with advanced (stage III or IV) NSCLC harbouring ALK gene rearrangement
Intervention	ALK Tyrosine Kinase Inhibitors, ALK inhibitors (Included crizotinib, ceritinib, alectinib, lorlatinib)
Comparators	• Chemotherapy • First generation ALK TKI (crizotinib)
Outcomes	i. Effectiveness • Overall survival (OS) • Progression free survival (PFS) • Overall response rate (ORR) • Health-related quality of life (HRQoL) ii. Safety • Adverse events iii. Economic impact • Cost-effectiveness • Cost-utility analysis • Cost-benefit analysis • Cost analysis • Any other measure of economic outcome iv. Organizational, social, ethical and legal implications
Study designs	HTA reports, systematic review with meta-analysis, systematic review, randomised controlled trial (RCT), and economic evaluation studies
Setting	Hospitals
English full text articles	

4.2.2 Exclusion criteria

a. Animal study
b. Laboratory study
c. Design: Narrative review, cohort, case-control, cross-sectional
d. Non-English full text articles
e. Studies involved ALK inhibition with other systemic treatment

Based on the above inclusion and exclusion criteria, study selection will be carried out independently by two reviewers. Disagreement will be resolved by discussion.

4.3 Critical Appraisal of Literature

The methodology quality of all retrieved literatures will be assessed using the relevant checklist of Cochrane Risk of Bias tool.

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

a. Details of methods and study population characteristics.
b. Details of interventions and comparators.
c. Details of individual outcomes for effectiveness, safety and cost associated with ALK TKIs for ALK positive advanced NSCLC patients

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion

4.4.2 Methods of data synthesis

Data on the effectiveness, safety and cost-effectiveness of ALK TKI for NSCLC will be presented in tabulated format with narrative summaries. Meta-analysis may be conducted for this Health Technology Assessment.

5.0 REPORT WRITING

6.0 REFERENCES

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APPENDIX 3: SEARCH STRATEGY

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Database: Ovid MEDLINE(R) ALL <1946 to June 28, 2022>
Search Strategy:

1 ANAPLASTIC LYMPHOMA KINASE/ (4107)
2 (alk adj1 kinase).tw. (3483)
3 (alk adj3 tyrosine kinase receptor).tw. (23)
4 (anaplastic adj2 lymphoma kinase).tw. (4441)
5 (anaplastic adj4 lymphoma receptor tyrosine kinase).tw. (89)
6 (cd246 adj1 antigen).tw. (0)
7 npm-alk.tw. (451)
8 ((nucleophosmin-anaplastic or nucleophosmin anaplastic) adj3 lymphoma kinase).tw. (107)
9 PROTEIN-TYROSINE KINASES/ (36378)
10 ((protein-tyrosine or tyrosine protein) adj2 kinase*).tw. (11014)
11 ((tyrosine or tyrosylprotein) adj1 kinase).tw. (81034)
12 ((tyrosine-specific or tyrosine specific) adj3 protein kinase*).tw. (374)
13 LUNG NEOPLASMS/ (245882)
14 (cancer* adj1 (lung or pulmonary)).tw. (187816)
15 (neoplasm* adj1 (lung or pulmonary)).tw. (2000)
16 (cancer adj3 lung).tw. (188532)
17 CARCINOMA, NON-SMALL-CELL LUNG/ (65206)
18 carcinoma, non small cell lung.tw. (103)
19 carcinoma, non-small cell lung.tw. (103)
20 ((non-small or nonsmall) adj3 lung cancer).tw. (71266)
21 ((non-small cell or non-small-cell) adj3 lung carcinoma).tw. (4794)
22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (405302)
23 PROTEIN KINASE INHIBITORS/ (55160)
24 (protein kinase adj2 inhibitor*).tw. (14733)
25 CRIZOTINIB/ (1584)
26 Crizotinib.tw. (2764)
27 "pf 02341066".tw. (39)
28 pf 2341066.tw. (24)
29 pf-02341066.tw. (39)
30 pf-2341066.tw. (24)
31 pf2341066.tw. (10)
32 Xalkori.tw. (32)
33 Ceritinib.tw. (533)
34 Lorlatinib.tw. (332)
35 Alectinib.tw. (758)
36 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (69328)
37 22 and 36 (23284)
38 limit 37 to (english language and humans) (19627)
39 limit 38 to "systematic review" (237)
40 limit 39 to yr="2012 -Current" (223)

APPENDIX 4: EVIDENCE TABLE

Available upon request to the author.

APPENDIX 5: LIST OF EXCLUDED STUDIES

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