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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 are diagnosed at an advanced stage. The 5-year observed survival rate is 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 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 Kuala Lumpur Hospital.

Objective/ aim

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

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metastatic ALK positive NSCLC

Methods

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

Systematic literature search was conducted 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. 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 and conclusion

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 in 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 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 demonstrated 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 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 crizo 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 BM. ALK inhibitors improved PFS compared with chemo or crizo 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 inhibitor compared to chemotherapy, or between next generation ALK inhibitor and crizotinib. The most common SAE reported were dyspnea 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 in 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 sensitive parameter 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. It was also found that reduction of drug price demonstrated a significant reduction of ICER.