EXECUTIVE SUMMARY
(Adapted from the report by ERNI ZURINA ROMLI)

Authors:
Dr. Erni Zurina Romli
Mr. Syful Azlie Md Fuzi
Miss Nurkhodrulnada Muhamad Lattepi
Dr. Izzuna Mudla Mohamed Ghazali

External Reviewers:

Prof. Dr. How Soon Hin
International Islamic University Malaysia

Dr. Irfhan Ali Hyder Ali
Head of Respiratory Services, MOH

Honorary Prof. Dr. Maznah Dahlui
University Malaya Medical Centre

Dr. Nurhayati Mohd Marzuki
Respiratory Medicine Institute, Hospital Kuala Lumpur

Prof. Dr. Sharifa Ezat Wan Puteh
National University of Malaysia

Dr. Sunita Bavanandan
Hospital Kuala Lumpur

For further information, please contact:

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya.

htamalaysia@moh.gov.my
Tel: 603 8883 1229
Available at the following website:
http://www.moh.gov.my

2022

Background

Lung cancer is the leading cause of global cancer-related death. In 2020, there were 2 million incident cases of lung cancer and 1.8 million deaths globally. In Malaysia, lung cancer is the third most common cancer, accounting for 9.8% of cancer cases. Most lung cancer cases in Malaysia are diagnosed at an advanced stage since symptoms do not manifest until they are locally advanced or there is metastatic disease. In comparison to other cancer types, lung cancer patients in Malaysia have the poorest 1-year (35.5%) and 5-year survival rates (11%). The most common type of lung cancer is non-small cell lung cancer (NSCLC) which accounts for about 85%–90% of all lung cancers. Two major types of NSCLC (WHO classification of tumours of the lung reference) can be distinguished into non-squamous and squamous cell carcinoma. Of all NSCLC, adenocarcinoma (non-squamous subtype) is the most common histological subtype of lung carcinomas diagnosed within the Malaysian population. The standard first-line therapy of patients with advanced NSCLC (stage IIIB and IV) without driver mutations and a good performance status [European Cooperative Oncology Group (ECOG) Performance Status 0-2] is a platinum-based doublet chemotherapy, achieving 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). Patients who are progressing on first-line therapy and relatively fit will be offered second-line chemotherapy. Docetaxel is recommended as second-line treatment. For patients who possess driver mutation, targeted therapy is currently recommended for all NSCLC histological subtypes. The emergence of immune-oncology drugs [also called immune checkpoint inhibitors (ICIs)] cause a dramatic change in the choice of treatment for patients with advanced NSCLC. Advancements in cancer immunotherapy have led to the approval of ICIs either as single agent or in combination with chemotherapy for the first- and second-line treatment of advanced NSCLC. The choice of ICIs is highly influenced by treatment history, genetic alterations, histology and level of programmed cell death ligand-1 (PD-L1) expression.

Technical features

Immune checkpoint inhibitors are a class of humanised immunoglobulins that target and inhibit receptors and their corresponding ligands responsible for the physiological 'off-switch' of immune cells. Their inhibition activates T-lymphocytes and enhances the adaptive anti-cancer immune response. To date, six ICIs: pembrolizumab, nivolumab, cemiplimab, durvalumab, atezolizumab and avelumab have been approved by the United States Food and Drug Administration (FDA), exclusively targeting the T cell co-inhibitory programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) signaling pathway, with clinical indications across 19 different cancer types.

The local landscape of immune checkpoint inhibitors therapy for advanced and metastatic NSCLC

Pembrolizumab, nivolumab, atezolizumab and durvalumab are currently registered for use in Malaysia. However, these ICIs and their companion/complementary testing are currently not subsidized by Malaysian government. Only a small number of patients receive the treatment through special channels. Majority of NSCLC patients in public hospitals have access to ICI treatment through participation in clinical trial. Those who can afford to self-pay or have private health insurance coverage mostly receive their ICI treatment in private hospital. Combination of the high costs of molecular testing and immune-oncologic drugs, immunotherapy with ICI is most difficult to afford out-of- pocket without private health insurance.

Policy Questions

1. Should immunotherapy (immune checkpoint inhibitors) be offered as a standard treatment option for patients with advanced and metastatic NSCLC in the Ministry of Health hospitals?

2. What is the best treatment strategy using immunotherapy (immune checkpoint inhibitors) in the management of PD-L1 positive patients with advanced and metastatic NSCLC in the Ministry of Health hospitals?

Objectives

1. To assess the comparative effectiveness and safety of immune checkpoint inhibitors in treating PD-L1 positive patients with advanced and metastatic NSCLC.
2. To determine the economic, organisational, ethical and social implications of implementing immunotherapy treatment options for this specific population of patients in the Ministry of Health hospitals.

Part A: Systematic Review of Literature

Methods

A comprehensive search was conducted on the following databases without any restriction on publication language and publication status. The Ovid interface: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non- Indexed Citations and Daily 1946 to July 27, 2022; Cochrane Library 2022 - Cochrane Database of Systematic Reviews – Cochrane Central Register of Controlled Trials (CENTRAL). Searches were also run in PubMed. Google was used to search for additional web-based materials and information. Additional articles were identified from reviewing the references of retrieved articles. Last search was conducted on 29 July 2022.

Results

A total of 2544 titles were identified through the Ovid interface and PubMed, and five were identified from references of retrieved articles. Following duplicate removal, appraising and applying the inclusion and exclusion criteria, 17 full text articles were eligible to be included for qualitative synthesis. The selected full text articles comprised of 12 network meta-analysis, one systematic review and meta-analysis, one systematic review and three economic evaluation studies.

Effectiveness

1. Clinical efficacy

Based on retrievable evidence, ICI-based treatment had a reduced risk of death [pooled hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.73 to 0.83, p<0.001] and disease progression (pooled HR 0.69, 95% CI 0.62 to 0.77, p < 0.001) in comparison to standard chemotherapy alone. A subgroup analysis of PD-L1 positive (PD-L1 expression ≥1%) population revealed lower death risk and disease progression when ICI-based treatment was compared to standard chemotherapy in a high PD-L1 (PD-L1 expression ≥50%) population (OS pooled HR 0.68, 95%CI 0.62 to 0.74, p < 0.00001; PFS pooled HR 0.58 (95%CI 0.53 to 0.63, p < 0.00001) than in a low PD-L1 (PD-L1 expression 1-49%) population (OS pooled HR 0.85, 95%CI 0.78 to 0.93, p=0.0005; PFS pooled HR 0.69, 95% CI 0.57 to 0.84, p < 0.00001]. The included network meta-analyses provided SUCRA ranking (ranking probability) of ICI-based treatments to be better treatment for the specific outcomes. For the **first line setting**, in a population of **advanced NSCLC with squamous histo-subtype having high PD-L1 expression**, atezolizumab in combination with chemotherapy (relative to standard chemotherapy: pooled HR 0.48, 95% CrI 0.29 to 0.80) and cemiplimab (relative to standard chemotherapy: pooled HR 0.48, 95% CrI 0.30 to 0.77) ranked as the highest ICIs with probability to be better treatment option in improving OS, while pembrolizumab in combination with chemotherapy (relative to standard chemotherapy: pooled HR 0.37, 95%CrI 0.24 to 0.58) ranked as the highest ICI for improving PFS. In a **low PD-L1 population**, pembrolizumab-chemotherapy combination scored the first ranking for the probability to be better ICI on both OS and PFS outcomes (relative to standard chemotherapy: pooled OS-HR 0.57, 95% CI 0.36 to 0.90, p=0.016 and pooled PFS-HR 0.56, 95% CI 0.32 to 0.97, p=0.040, respectively). In a population of **advanced NSCLC with non-squamous histo-subtype**

having **high PD-L1 expression**, pembrolizumab-chemotherapy combination (relative to standard chemotherapy: pooled HR 0.42, 95% CrI 0.26 to 0.68) and pembrolizumab monotherapy (pooled HR 0.58, 95% CrI 0.41 to 0.83) ranked as top two ICI-based treatments for OS outcome, while pembrolizumab-chemotherapy combination ranked among the highest for the outcome of PFS (relative to standard chemotherapy:pooled HR 0.36, 95% CrI 0.25 to 0.52). In **low PD-L1 population**, pembrolizumab-chemotherapy (relative to standard chemotherapy: pooled HR 0.55, 95% CrI 0.34 to 0.89) combination ranked the highest for the OS outcome, while for PFS outcome pembrolizumab-chemotherapy (relative to standard chemotherapy: pooled HR 0.55, 95% CrI 0.31 to 0.81) combination ranked second after sintilimab-chemotherapy combination (not FDA-approved for advanced NSCLC).

For second and subsequent line setting, in a population of PD-L1 positive advanced NSCLC, pembrolizumab, nivolumab and atezolizumab monotherapy showed statistically significant improvement in OS compared to the standard second-line chemotherapy, docetaxel. While nivolumab and pembrolizumab monotherapy had significant PFS benefit over docetaxel, atezolizumab monotherapy displayed no significant reduction in disease progression compared to docetaxel. Pooled results from the indirect comparison between pembrolizumab, nivolumab and atezolizumab monotherapy in second-line setting revealed no statistically significant differences in OS and PFS in PD-L1 positive population.

2. Patient-reported outcome

Patient-reported outcomes (PROs) are aimed to capture quality of life (QoL) in a comprehensive way from the patient's point of view. The PD1/PD-L1 inhibitor given as monotherapy, the pooled between-groups difference of mean change from baseline to 12 weeks of follow-up was 4.6 (95% CI, 2.8-6.4), and the mean change from baseline to 24 weeks of follow-up was 6.1 (95% CI, 4.2-8.1), significantly favouring PD1/PD-L1 inhibitors. There was no statistically significant difference in the pooled mean change of PD1/PD-L1 inhibitors combined with chemotherapy from baseline to 12 weeks and 24 weeks of follow-up. The time to deterioration (TTD) was significantly longer in the immunotherapy-containing groups compared with standard chemotherapy group [HRs of 0.80 (95%CI 0.70 to 0.91)] for ICIs as monotherapy and 0.89 (95%CI 0.78 to 1.00) for ICIs plus chemotherapy.

Safety

The overall mean incidence of all-grade adverse events of ICI-based treatment reported in clinical trials was 1.66% (95%CI 1.47% to 1.86%) and the mean incidence of serious adverse events (grade ≥3) was 0.11% (95%CI 0.08% to 0.14%). A lower risk of TRAEs compared to chemotherapy alone was found with ICI monotherapy (RR 0.28, 95% CrI 0.21 to 0.38) and dual ICI combinations (RR 0.52, 95% CrI 0.35 to 0.77). a significantly higher risk of any treatment related adverse events (TRAEs) [relative risk (RR) 1.99, 95% CrI 1.34 to 2.99]. Nivolumab monotherapy had the highest probability to be the treatment with better safety profile (SUCRA = 99%). Addition of chemotherapy to pembrolizumab, atezolizumab and nivolumab worsened their safety profile. Fatal adverse events (FAEs) of ICIs are relatively uncommon. The incidence of FAEs was 0.65% (95%CI 0.31 to 1.07, I^2 = 50.2%) in ICI monotherapy and 2.01% (95%CI 1.42 to 2.69, I^2 = 5.9%) in the combination therapy (ICI and chemotherapy). While fatal events in chemotherapy were mainly derived from myelosuppression and infection, in immunotherapy, FAEs were mainly caused by non-infectious pneumonitis (immune-related adverse events), which might result from the overactivation of immune system.

Cost/Cost-effectiveness

1. *Pembrolizumab*

In majority of studies, pembrolizumab was more economical than traditional chemotherapy regimens. The results also suggested that pembrolizumab improved quality-adjusted expectancy and could be considered a cost-effective option compared with docetaxel for patients with PD-L1 expression. One study found that first-line pembrolizumab is likely to be cost-effective within the US but not in the UK compared with platinum-based chemotherapy. This difference was due to different willingness to pay (WTP) thresholds (US: $100,000; UK: $42,048) as the incremental cost-effectiveness ratio (ICER) values of both countries were close to each other in nearly all sensitivity and dependency analyses. In Switzerland, as a first line setting treatment, pembrolizumab monotherapy was cost-effective [ICER of CHF 68,580/ quality-adjusted life year (QALY)] from the Swiss healthcare payer perspective, whereas pembrolizumab plus chemotherapy was not (ICER CHF 475,299/QALY) (WTP threshold of CHF 100,000 per QALY gained). While in Taiwan, pembrolizumab monotherapy (ICER NT$416,102/QALY) was more cost effective than nivolumab (ICER NT$1,572,912/QALY) and atezolizumab (NT$1,580,469/QALY) compared to docetaxel as a second-line regimen for patients with previously treated advanced NSCLC at WTP of NT$2,221,930 (US$24,408) in Taiwan [from the perspective of Taiwan National Health Insurance Administration (NHIA)].

2. *Nivolumab*

In majority of the cost-effectiveness studies (Canada, Australia, Switzerland and China), nivolumab was not a cost-effective option in second line setting. However, nivolumab (ICER NT$1,572,912/QALY) was considered as cost-effective option from the perspective of Taiwan National Health Insurance Administration [WTP threshold of NT$2,221,930 (US$24,408)].

3. *Atezolizumab*

One study concluded that atezolizumab is a cost-effective second-line therapeutic option in Canada for the treatment of patients with advanced NSCLC. However, atezolizumab combination therapy was not cost-effective when used as first-line treatment for NSCLC. In addition, atezolizumab monotherapy was estimated not to be cost-effective compared to platinum-based chemotherapy (ICER US$170,730 per QALY) in the first-line treatment of patients with NSCLC with high PD-L1 expression from US payer perspective (WTP threshold of US$100,000/QALY and US$150,000/QALY).

Part B: Economic Evaluation

A cost-effectiveness analysis (CEA) was conducted from the perspective of Ministry of Health (MOH), Malaysia, in which a three-health states Markov model with three-week cycle and a lifetime horizon was constructed and analysed using Microsoft Excel 2019. The objective of this CEA is to assess the incremental cost-effectiveness ratio (ICER) between PD-1/L1 inhibitors and conventional chemotherapy in the first- and second-line treatment settings for advanced metastatic NSCLC. The primary outcomes included total cost and quality-adjusted life years (QALYs) gained for each intervention in consideration. An annual discount rate of three per cent was applied to both costs and outcomes estimated.

Input on the treatment effects was drawn from the systematic review carried out in Section A of this report. Meanwhile, costs for drug acquisition and disease management were based on available local data. Health utility values for progression free and progressive disease states and other key parameters applied to the model were sourced from previously published studies. As there was no explicit national cost-effectiveness threshold available, one time of the per capita gross domestic product (GDP) of Malaysia in 2021 was used in this analysis (MYR 47,439/QALY).

In the first-line setting, the ICERs generated were reported according to the two most common histological subtypes of NSCLC. In squamous NSCLC, combination of atezolizumab and chemotherapy has shown the lowest ICER at around MYR 142,000 per QALY gained in high PD-L1 expressors when compared to conventional platinum-based chemotherapy. In non-squamous NSCLC, the lowest generated ICER was for the combination of pembrolizumab and chemotherapy at around MYR 264,000 per QALY gained. None of these interventions was found to be cost-effective at the specified threshold.

Likewise, all interventions in the second-line setting were not cost-effective at the specified threshold. The ICERs estimated ranged from around MYR 171,000 to MYR 232,000 per QALY gained. Two scenario analyses were also performed, in which provision of shorter treatment duration and patient co-payment for one course of treatment were explored for both lines of treatment. Nevertheless, none of the interventions was cost-effective despite apparent reduction in the total costs and ICERs.

One-way sensitivity analysis was performed to assess key drivers that mostly impacted the estimated ICERs. Drug cost and health utility value for health states associated with each treatment were noted to show remarkable impact on the ICERs of the first-line ICIs. Meanwhile, drug cost and health utility value for health states in the comparator arm for the second-line ICIs appeared to greatly influence the estimated ICERs.

CONCLUSIONS

The ICI-based treatment was associated with higher survival and health-related quality of life benefit than standard chemotherapy in PD-L1 positive advanced NSCLC population. The benefits were more prominent in high PD-L1 expression population. In first line setting, pembrolizumab-chemotherapy has the highest probability to be better treatment option for PD-L1 positive population with non-squamous histo-subtype. Atezolizumab-chemotherapy combination had the highest probability to be better treatment option for those with high PD-L1 expression advanced NSCLC squamous subtype. In pretreated population, nivolumab monotherapy had demonstrated the highest probability to be better treatment compared to others. In term of safety, ICI monotherapy had better safety profile compared to ICI-chemotherapy combination and standard chemotherapy based on the occurrence of serious adverse events. Fatal adverse event in immunotherapy was mainly associated with non-infectious pneumonitis (immune-related adverse event). Evidence from economic evaluation studies tend to suggest that ICI-based treatment is likely to be cost-effective in high-income countries and countries with WTP of ≥ USD100,000. Results from the conducted cost-effectiveness study indicate that PD-1/PD-L1 checkpoint inhibitors are unlikely to be cost-effective first- and second-line treatment options for Malaysians suffering from advanced NSCLC, regardless of PD-L1 expression status.

POLICY RECOMMENDATIONS

Based on current evidence, pembrolizumab either as monotherapy or in combination with chemotherapy should be offered as standard treatment for patients with high PD-L1 expression non-squamous advanced NSCLC in the first line setting. Competitive pricing strategy and provision of effective policies on high-cost drugs are crucial in meeting the treatment needs.