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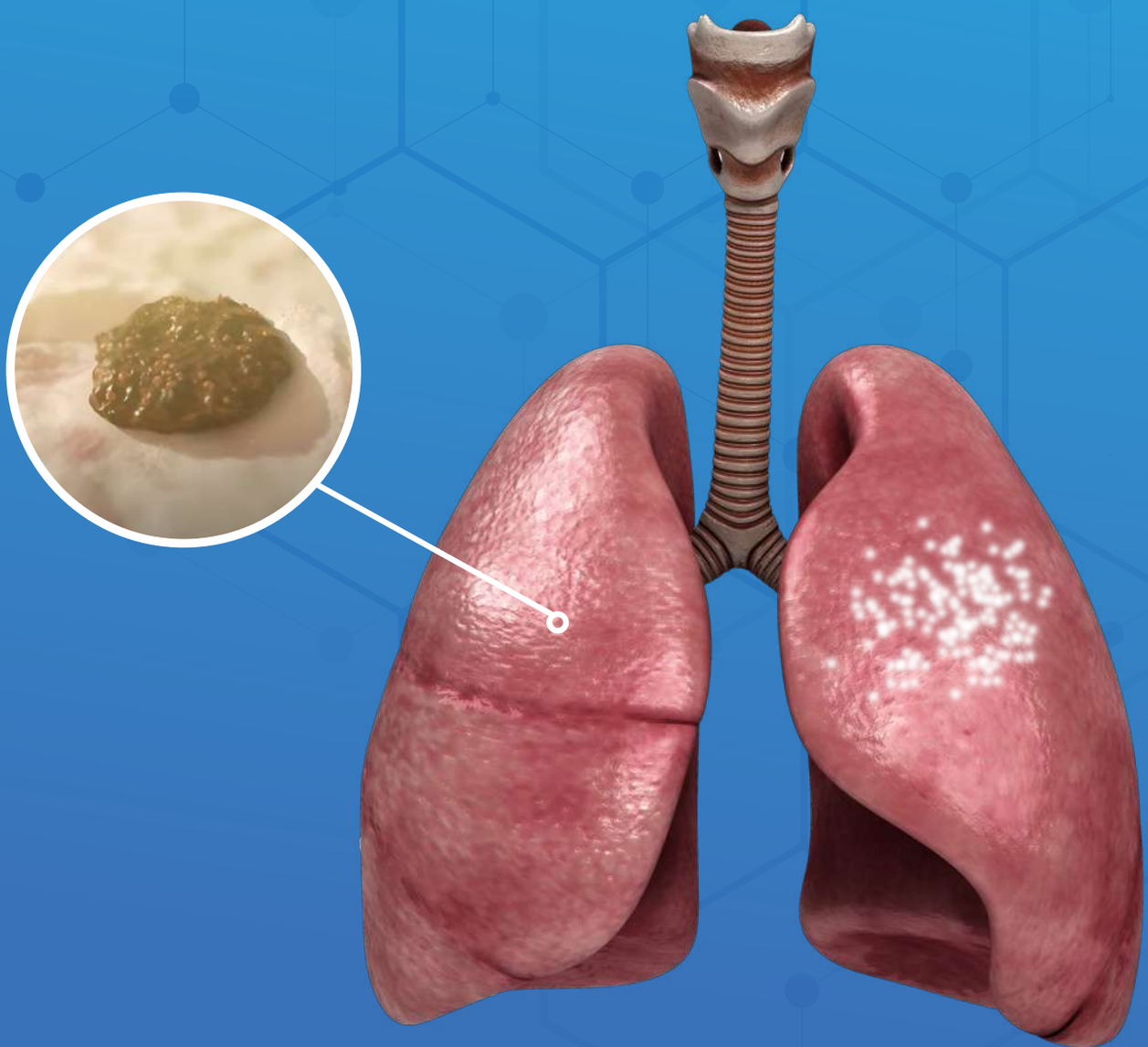
HEALTH TECHNOLOGY ASSESSMENT REPORT



IMMUNOTHERAPY FOR PD-L1 POSITIVE ADVANCED NON-SMALL CELL LUNG CANCER

Malaysian Health Technology Assessment Section

Medical Development Division
Ministry of Health Malaysia

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Malaysian Health Technology Assessment Section (MaHTAS)
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EXECUTIVE SUMMARY

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.

<u>Safety</u>

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 $\geqslant$ 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.

TABLE OF CONTENTS

ABBREVIATION

1ySR	1-year survival rate
2ySR	2-year survival rate
AEs	adverse events or adverse effects
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
CASP	Critical Appraisal Skills Programme
CI	confidence interval
CHF	Confoederatio Helvetica Franc
CT	computed tomography
CTCAE	common terminology criteria for adverse events
CTLA-4	cytotoxic T-lymphocyte-associated protein-4
CXR	chest radiography
ECOG	European Cooperative Oncology Group
EMA	European Medicines Agency
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-3L	EuroQol Health-Related Quality of Life 5-Dimension, 3-Level
FAEs	fatal adverse events
FFPE	formalin-fixed and paraffin- embedded
FNAs	fine-needle aspirations
GHS	global health status
HR	hazard ratio
HRQoL	health-related quality of life
HTA	health technology assessment
IHC	immunohistochemistry
ICER	incremental cost-effectiveness ratio
ICI	immune checkpoint inhibitor
irAEs	immune-related adverse events
KM	kaplan meier
MaHTAS	Malaysian Health Technology Assessment Section
MNCR	Malaysia National Cancer Registry
MOH	Ministry of Health
mOS	median overall survival
MYR	Malaysian Ringgit
NSCLC	non-small cell lung carcinoma
NTD	New Taiwan dollar
ORR	objective response rate
OS	overall survival
PD	progressive disease

PD-1	programmed cell death protein 1
PD-L1	programmed cell death ligand 1
PF	progression-free
PFS	progression free survival
PROs	patient-reported outcomes
PS	performance status
QALY	quality adjusted life year
QoL	quality of life
RCT	randomised controlled trial
ROBIS	Risk of Bias in Systematic reviews
RWE	real world evidence
SUCRA	surface under the cumulative ranking
TC	tumour cells
TPS	tumor proportion score
TRAEs	treatment related adverse events
TTD	time to deterioration
VAS	visual analogue scale
WTP	willingness-to-pay
US FDA	United States Food and Drug Administration

1.0 BACKGROUND

1.1 Burden of Disease

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. [1] In Malaysia, lung cancer is the third most common cancer, accounting for 9.8% of cancer cases. A total of 11,256 cases of trachea, bronchus and lung cancers were registered in the period of 2012-2016 compared with 10,608 cases in 2007-2011 report. Age-standardised rates show that incidence is about twice as high in men (13.2 cases per 100,000 persons) than in women (5.9 cases per 100,000 persons). [2] Lifetime risk for Malaysian men and women were reported to be 1 in 60 and 1 in 138, respectively. [2] The incidence increased with age, highest at the age of 70 and above. [2] 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. [2, 3] According to Malaysia National Cancer Registry Report, between 2012 to 2016, 78.1% of male and 81.3% of female lung cancer patients were diagnosed with stage IV lung cancer. [2] 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. [4] 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 stage-specific 1- and 5-year survival rates are 39.4% 1-year survival, 7.5% 5-year survival for stage III and 29.6% 1-year survival, 6.3% 5-year survival for stage IV. [5] 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.[6] Of all NSCLC, adenocarcinoma (non-squamous subtype) is the most common histological subtype of lung carcinomas diagnosed within the Malaysian population. [7]

1.2 Current Treatment [8-12]

The most used treatment modalities for NSCLC are radiation therapy, surgery and systemic therapy. Based on the tumour stage, histology (non-squamous or squamous), presence or absence of driver mutations and the overall medical condition of a patient, these treatments can be applied alone or in combination. For patients who possess **driver mutation**, targeted therapy is currently recommended for all NSCLC histological subtypes. 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. 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 treatments 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. (Figure 1)

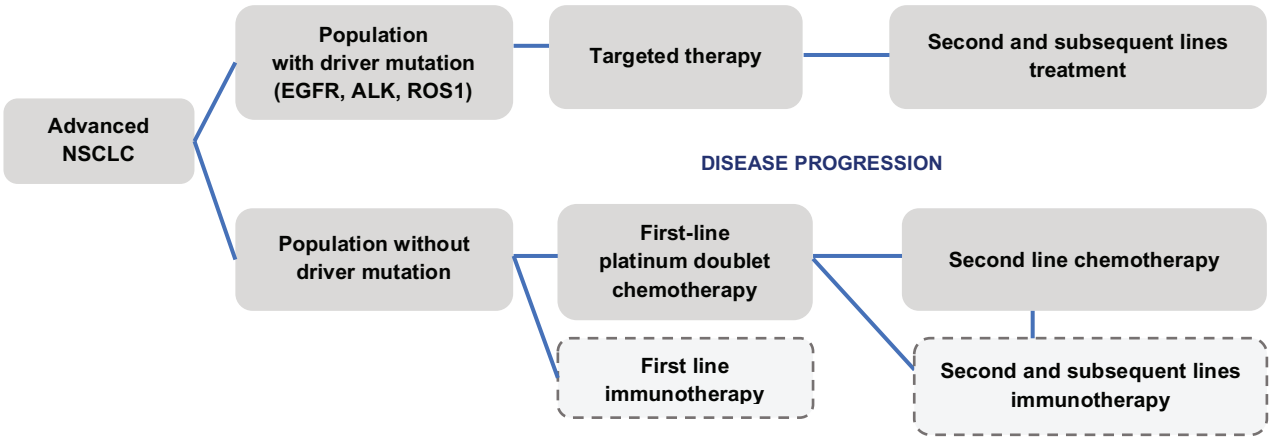
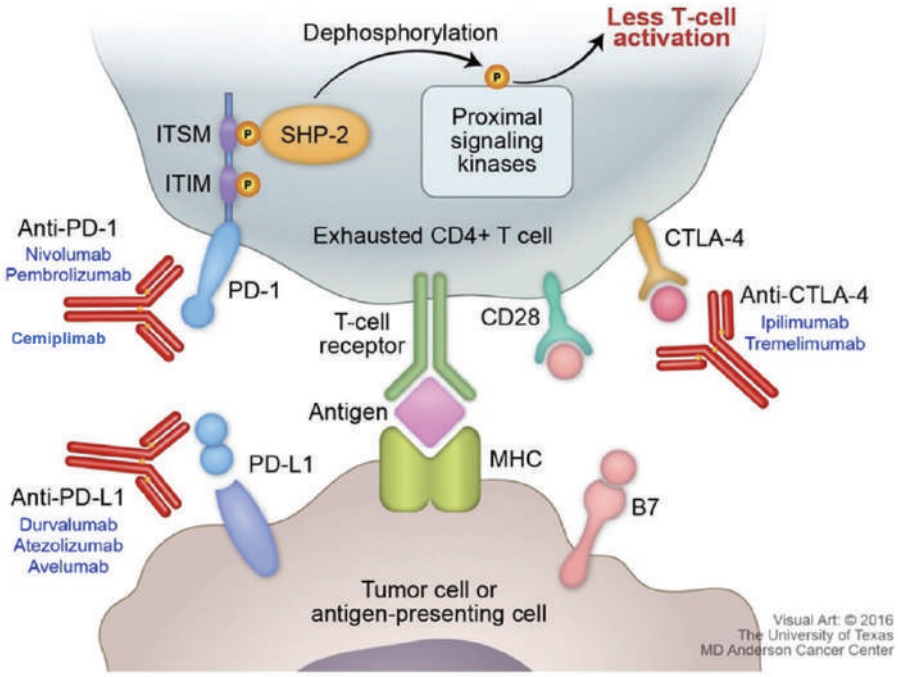


Figure 1: Populations and therapies of focus

2.0 TECHNICAL FEATURES

2.1 Description of Technology: Immune Checkpoint Inhibitors

One of the theories of tumour invasion and metastasis is immune evasion. The immune system has the ability to suppress tumour growth by eliminating cancer cells. However, tumour cells can escape the immune system attack by forming immune checkpoints.[13] The most studied immune checkpoint receptors are the inhibitory receptors anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1).[14] Blocking the immune checkpoints can activate the immune system and prevent tumour cell evasion. This discovery has introduced a new era in cancer treatment.[13] Immune checkpoint inhibitors (ICIs) are a class of humanised immunoglobulins that target and inhibit receptors and their corresponding ligands responsible for the physiological 'off-switch' of immune cells.[11] Their inhibition activates T-lymphocytes and enhances the adaptive anti-cancer immune response. To date, six ICIs have been approved by the United States (US) 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. (Figure 2) [15] Five of these PD-1/PD-L1 checkpoint inhibitors (pembrolizumab, nivolumab, atezolizumab, durvalumab and cemiplimab) have approved indications for NSCLC as shown in Table 1.[15, 16]



*ITSM=immunoreceptor tyrosine-based switch motif; ITIM=immunoreceptor tyrosine-based inhibitory motif; CD28=cluster of differentiation 28; MHC=major histocompatibility complex; SHP-2=Src homology 2 (SH2) domain containing non- transmembrane PTP.

Figure 2: PD-1/PD-L1 pathway and immunotherapy targets[17]

Table 1: Immune Checkpoint Inhibitors (ICIs) Targeting PD-1/PD-L1 Pathway Approved by FDA for Use in NSCLC [15, 16, 18]

PD-1/PD-L1 Inhibitor (*Brand name*)	FDA-approved indication	Date of approval
Pembrolizumab (*Keytruda*) - humanised, IgG4 monoclonal antibody against PD- 1 receptor	Metastatic NSCLC patients who progressed after platinum-based therapy or epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-targeted therapy and are positive for PD-L1	2 October 2015
	First-line treatment for metastatic NSCLC with high PD-L1 expression (≥ 50%) without EGFR or ALK mutation	24 October 2016
	First-line treatment in combination with pemetrexed and carboplatin for metastatic non-squamous NSCLC without EGFR or ALK mutation, regardless of PD-L1 expression	10 May 2017
	First-line treatment in combination with carboplatin with paclitaxel/nab-paclitaxel for metastatic squamous NSCLC, regardless of PD-L1 expression	30 Oct 2018

PD-1/PD-L1 Inhibitor (*Brand name*)	FDA-approved indication	Date of approval
	First-line monotherapy for patients with stage 3 NSCLC who cannot undergo surgical resection/ chemoradiation or metastatic NSCLC with PD-L1 expression ≥1% and no EGFR or ALK mutation	11 April 2019
Nivolumab (*Opdivo)* - human immunoglobulin (Ig) G4 antibody against PD-1 receptor	**Squamous** NSCLC with progression after platinum-doublet chemotherapy, regardless of PD-L1 expression	4 Mac 2015
	Metastatic non-squamous NSCLC with progression on first-line platinum-based chemotherapy	10 October 2015
Atezolizumab (*Tecentriq)* - human monoclonal IgG1 antibody directed against PD-L1	**Metastatic NSCLC** with progression on platinum-based chemotherapy, and in progression on targeted therapy in patients with EGFR or ALK abnormalities.	18 October 2016
	Metastatic non-squamous NSCLC without EGFR or ALK mutation in combination with carboplatin, paclitaxel, and bevacizumab	6 December 2018
	First-line monotherapy for patients with metastatic NSCLC whose tumours have high PD-L1 expression (PD-L1 stained ≥ 50% of tumour cells [TC ≥ 50%] or PD-L1 stained tumour-infiltrating immune cells [IC] covering ≥ 10% of the tumour area [IC ≥ 10%]), as determined by an FDA-approved test, with no EGFR or ALK genomic tumour aberrations.	18 May 2020
Durvalumab (*Imfinzi)* - selective, high- affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80	**Surgically unresectable stage III** NSCLC with no progression after treatment with chemoradiation (concurrent platinum-based chemotherapy and radiation therapy)	16 February 2018
	In combination with tremelimumab (Imjudo, AstraZeneca Pharmaceuticals) and platinum-based chemotherapy for adult patients with metastatic NSCLC with no sensitizing EGFR mutation or ALK genomic tumour aberrations.	10 November 2022
Cemiplimab (*Libtayo*) - human immunoglobulin (Ig) G4 antibody against PD-1 receptor	**First-line treatment** for patients with NSCLC whose tumours have high PD-L1 expression [Tumour Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations, and is: - locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or - metastatic	22 February 2021

2.2 PD-L1 Testing

2.2.1 Global and local prevalences of positive PD-L1 expression in advanced NSCLC population

The PD-L1 expression on immune cells or tumour cells has been shown to be an effective predictive biomarker for response to ICI treatment.[19-23] The PD-L1 expression was reported as tumour proportion score (TPS), which is the percentage of viable tumour cells showing partial or complete membrane staining at any intensity, relative to all viable tumour cells. The presence of PD-L1 expression (**positive PD-L1 expression**) is when the TPS is ≥1%, which is further subdivided into **low PD-L1 expression** (TPS = 1 – 49%) and **high PD-L1 expression** (TPS ⩾ 50%). The EXPRESS study is a global, multicentre study across 18 countries, aimed to determine real-world prevalence of PD-L1 expression in tumour cells of patients with advanced or metastatic NSCLC.[24] The study reported the prevalence of positive PD-L1 expression was 52% and 22% of patients had high PD-L1 expression. The prevalence of PD-L1 expression was similar across geographic regions The percentages of patients with PD-L1 TPS ⩾ 50% and TPS ⩾ 1%, respectively were: 22%/52% in Europe; 22%/53% in Asia Pacific; 21%/47% in the Americas, and 24%/55% in other countries. Among those who were negative for both EGFR mutation and ALK translocation, 53% had PD-L1 TPS ⩾ 1% and 27% had PD-L1 TPS ⩾ 50%. The prevalence of PD-L1 expression across histological subtypes was also similar. The percentages of patients with PD-L1 TPS ⩾ 50% and TPS ⩾ 1%, respectively were 57%/ 23% in squamous NSCLC and 51%/22% in non-squamous NSCLC. [24] A local multicentre study involving public, private and university hospitals reported 61% of their participants with NSCLC tested positive for PD-L1 expressor gene.[3] Among those with PD-L1 expressor gene, 28% was categorised as having high PD-L1 expression (PDL-1 TPS ⩾ 50%). These findings were consistent with the pattern of prevalence of PD-L1 expression in EXPRESS study. However, the Malaysian data showed that tumours with driver mutation were more likely to have no PD-L1 expression [crude odd ratio (OR) 0.579, 95% confidence interval (CI) 0.399 to 0.840, p=0.004], which in EXPRESS study no difference was seen in PD-L1 expression between tumours with driver mutations and those without.

There was no statistical difference in PD-L1 expression between the different ethnic groups.[3]

2.2.2 PD-L1 immunohistochemistry assays

Currently, PD-L1 immunohistochemistry (IHC) is the only testing method to guide the administration of anti–PD-1/PD-L1 checkpoint inhibitors in NSCLC patients.[25] Companion diagnostics, which (per the US Food and Drug Administration (FDA) definition), provide information, often obtained in vitro, that is "essential for the safe and effective use of a corresponding drug or biologic product".[26] While complementary (or co-diagnostic) tests that may be used in treatment selection but are not considered essential for safe and effective use of the corresponding therapy in practice. The key difference between companion and complementary diagnostics is that companion diagnostics are bound to a specific drug within its approved label but complementary or co-diagnostics may be associated with particular drugs but are not included in the licensing indications for those drugs.[26] The IHC-22C3 for pembrolizumab[27] and cemiplimab[16], as well as Ventana PD-L1 (SP142) assay for atezolizumab[18] are currently the only FDA-approved companion diagnostic for PD-1/PD-L1 targeted immunotherapies. In some countries, PD-L1 testing by IHC is mandatory for certain indications before ICIs may be prescribed. In the US, Europe, Canada and Japan, prescription of pembrolizumab as first line monotherapy in NSCLC requires evidence of PD-L1 staining on at least 50% of the tumour cells.[28] In Australia, the product information for pembrolizumab monotherapy (first or second line) states the patient's tumour should have a PD-L1 TPS of at least 1%, with treatment guidelines recommending pembrolizumab monotherapy for patients with PD-L1 TPS ≥ 50% and without driver mutations.[29]

As of February 2021, there are five commercially available companion or complementary diagnostic assays for PD-L1 expression level that have been approved to identify patients across seven tissue types.[15] The range of companion/complementary PD-L1 IHC assays which have been approved for its paired drug is shown in Table 2. Formalin-fixed and paraffin- embedded (FFPE) sections of biopsies or resected specimens and cell blocks of

fine-needle aspirations (FNAs) or effusion specimens can be used for IHC testing of PD-L1. Liquid biopsies (utilising circulating tumour cells) are not recommended currently.[30] The expanded use of diagnostic assay across different immuno-oncologic products and tumour types is also not recommended.[15] These different assays have been developed independently using different diagnostic antibodies, protocols, reagents, cell types, and detection systems, therefore, associated with specific drugs. The scoring metrics and PD-L1 thresholds that determine a biomarker-positive patient differs across different assays.[25, 30]

2.2.3 Influence of training *on* PD-L1 interpretation

Interpretation of an immunohistochemical analysis is subjected to some variability between readers. Various international harmonization and concordance studies found that trainings are necessary to guarantee consistency and quality in the scoring and interpretation of PD-L1 expression patterns. [31, 32] Discrepancies in the interpretation of PD-L1 staining has been shown can be improved with standardised intensive training for practising pathologists. A one-day reader training of TPS scoring in NSCLC among certified pathologists, utilising combination of web-based and classroom-style training module resulted in high overall percentage agreement (85-95%) of inter-reader concordance for PD-L1 tumour cells (TC) scoring at clinically relevant cut-offs (≥1%, ≥25% and ≥ 50%). The training consisted of a one-hour presentation covering the biology of PD-L1, development of the assay, cellular expression, and strategies to optimally assess expression in NSCLC. This followed with practical session assessing PD-L1 staining sample set.[31]

Table 2: PD-L1 expression testing, paired ICI, regulatory approvals and technical aspects for evaluation [33-36]

Diagnostic Assay (Manufacturer)	Paired ICI	Type of diagnostic testing (FDA approval date)	EMA status	PD-L1 diagnostic Ab clone (Ab host species)	PD-L1 binding domain	Platform; Detection Kit	Definition of PD-L1 positivity	Cut-off value of minimum viable TC
PD-L1 IHC 22C3 pharmDx (Dako North America, Inc./ Merck)	Pembrolizumab	Companion (02/10/2015)	CE mark	22C3 (mouse)	Extracellular	Autostainer Link 48; Envision FLEX	Cut-off for positivity: TPS ≥ 1% TC Cut-off for indication: **Pembrolizumab**: TPS ≥ 50% TC for first line; TPS ≥ 1% TC for second line **Cemiplimab**: TPS ⩾ 50% TC [33]	100 TC
	Cemiplimab	Companion (22/02/2021)						
PD-L1 IHC 28-8 pharmDx (Dako North America, Inc./ Merck)	Nivolumab	Complementary (15/05/2020)	CE mark	28-8 (rabbit)	Extracellular	Autostainer Link 48; Envision FLEX	TPS ≥ 1% TC	100 TC
Ventana **PD-L1 (SP142) Assay** (Ventana Medical Systems, Inc./ Roche)	Atezolizumab	Companion (02/07/2018)	CE mark	SP142 (rabbit)	Cytoplasmic	BenchMark ULTRA; Optiview	TC ⩾ 50% or IC ⩾ 10%	50 TC
Ventana **PD-L1 (SP263) Assay** (Ventana Medical Systems, Inc./ Roche)	Durvalumab	Complementary (01/05/2017- *FDA approval only for urothelial carcinoma)*	CE mark for nivolumab, pembrolizumab, atezolizumab in NSCLC and durvalumab in urothelial carcinoma	SP263 (rabbit)	Extracellular	BenchMark ULTRA; Optiview	TPS ⩾25% TC	100 TC
	Atezolizumab	Complementary (15/10/2021)						
PD-L1 IHC 73-10 pharmDx (Dako North America, Inc./ Roche)	Avelumab	Complementary (*Research use only*)	Not available	73-10 (rabbit)	Extracellular	Autostainer Link 48; Envision FLEX	TPS ≥ 1% TC	undefined

CE Conformite Europeenne; **TPS** Tumor Proportion Score; **TC** tumour cells; **IC** immune cells; **FDA** Food and Drug Administration; **EMA** European Medicines Agency; **Ab** antibody

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

In Malaysian public hospitals, patients with advanced and metastatic NSCLC without driver mutations are commonly treated with platinum doublet chemotherapy.[12] Combination of either pembrolizumab and atezolizumab with chemotherapy is approved for first-line treatment of advanced NSCLC regardless of PD-L1 expression, and pembrolizumab alone is approved for the first line in patients with PD-L1 expression of at least 1%.[3, 37] While atezolizumab monotherapy is approved for the first line in patients with high PD-L1 expression (PD-L1 TPS $\geqslant$ 50%).[18] Durvalumab is registered for use in patients with stage III lung cancer after chemo-radiotherapy. Atezolizumab, nivolumab and pembrolizumab are approved as second-line treatments in patients who fail chemotherapy.[37] These ICIs and their companion/complementary testing are currently not subsidized by Malaysian government.[3] 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.[3] Combination of the high costs of molecular testing and immune-oncologic drugs, ICI is most difficult to afford out-of- pocket without private health insurance. Immune checkpoint inhibitors approved in Malaysia for advanced/metastatic NSCLC as well as their reimbursement status, are listed in Table 3. The current review evaluated three ICIs approved for use in Malaysia. Durvalumab was excluded from the review as the intended NSCLC population for its use differs from the population of interest in this review.

Table 3: Immune Checkpoint Inhibitors Approved in Malaysia for Advanced/Metastatic NSCLC and Their Reimbursement Status [18, 37]

Immune Checkpoint Inhibitor (distributor)	Approved as First Line Treatment	Approved as Second Line Treatment	Available for free at public hospital	Reimbursement (Private Insurance)
Pembrolizumab (*MSD Malaysia*)	**Yes**	**Yes**	**No**	**Yes**
Nivolumab (*Bristol Myers Squibb – distributed by DKSH Malaysia)*	**No**	**Yes**	**No**	**Yes**
Atezolizumab (*Roche*)	**Yes**	**Yes**	**No**	**Yes**
Durvalumab (*AstraZeneca*)	**Yes**	**No**	**No**	**Yes**

3.0 POLICY QUESTIONS

3.1 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?

3.2 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?

4.0 OBJECTIVES

4.1 To assess the comparative effectiveness and safety of locally available immune checkpoint inhibitors in treating PD-L1 positive patients with advanced and metastatic NSCLC.

4.2 To determine the economic, organisational, ethical and social implications of implementing immunotherapy treatment options for patients with advanced and metastatic NSCLC in the Ministry of Health hospitals.

Research Questions

i. How effective and safe are the immune checkpoint inhibitors in the treatment of PD-L1 positive patients with advanced and metastatic NSCLC?

ii. How cost-effective are the immune checkpoint inhibitors for the treatment of advanced and metastatic NSCLC?

iii. What are the organisational, ethical and social implications of implementing this treatment option in Ministry of Health hospitals?

5.0 PART A: SYSTEMATIC REVIEW OF LITERATURE

5.1 METHODS

5.1.1 Searching

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.

Appendix 3 showed the detailed search strategies.

5.1.2 Study selection

Two review authors (EZ and SA) screened the titles and abstracts retrieved by electronic searches independently. The full texts for all relevant studies were obtained and checked for the eligibility of each study against review eligibility criteria (the inclusion and exclusion criteria). The final selection of articles was done by the lead reviewer (EZ) and reviewed by second reviewer (SA). Any discrepancies between review authors were resolved by discussion to reach consensus. The third review author (IM) was included to reach consensus if required. Relevant articles were critically appraised using The Cochrane Collaboration's tools. All full text articles were graded according to US/Canadian Preventive Services Task Force (Appendix 1). Data were extracted and summarised in evidence table as in Appendix 4.

The inclusion and exclusion criteria were:

Inclusion criteria

Population	Patient with advanced and metastatic (stage IIIB / IV) NSCLC who are positive for PD-L1 expression
Interventions	Immune Checkpoint Inhibitors (ICI) with indication for population of interest & available locally (Atezolizumab, Pembrolizumab, Nivolumab), either as single agent, or in combination with chemotherapy
Comparators	Standard chemotherapy
Outcomes	i. Effectiveness: Survival outcomes - overall survival (OS) - progression free survival (PFS) - objective response rate (ORR) Health-related quality of life (HRQoL) outcomes ii. Safety: Adverse events iii. Economic implication (cost, cost-effectiveness) iv. Organisational, ethical and social issues
Study design	Health Technology Assessment, Systematic Review, RCT, non-randomized trial, cohort, case-control, cross-sectional and economic evaluation studies
	English full text articles

Exclusion criteria

Study design	Studies conducted in animals, case series or case reports
	Non English full text articles

5.2 RESULTS

5.2.1 Selection of included studies

A total of 2544 titles were identified through the Ovid interface and PubMed, and five were identified from references of retrieved articles. After removal of duplicate articles, 1374 titles were screened using the inclusion and exclusion criteria. Of these, 144 relevant abstracts were retrieved in full text. After reading, appraising and applying the inclusion and exclusion criteria, only 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. The selection of studies is as shown on Figure 3.

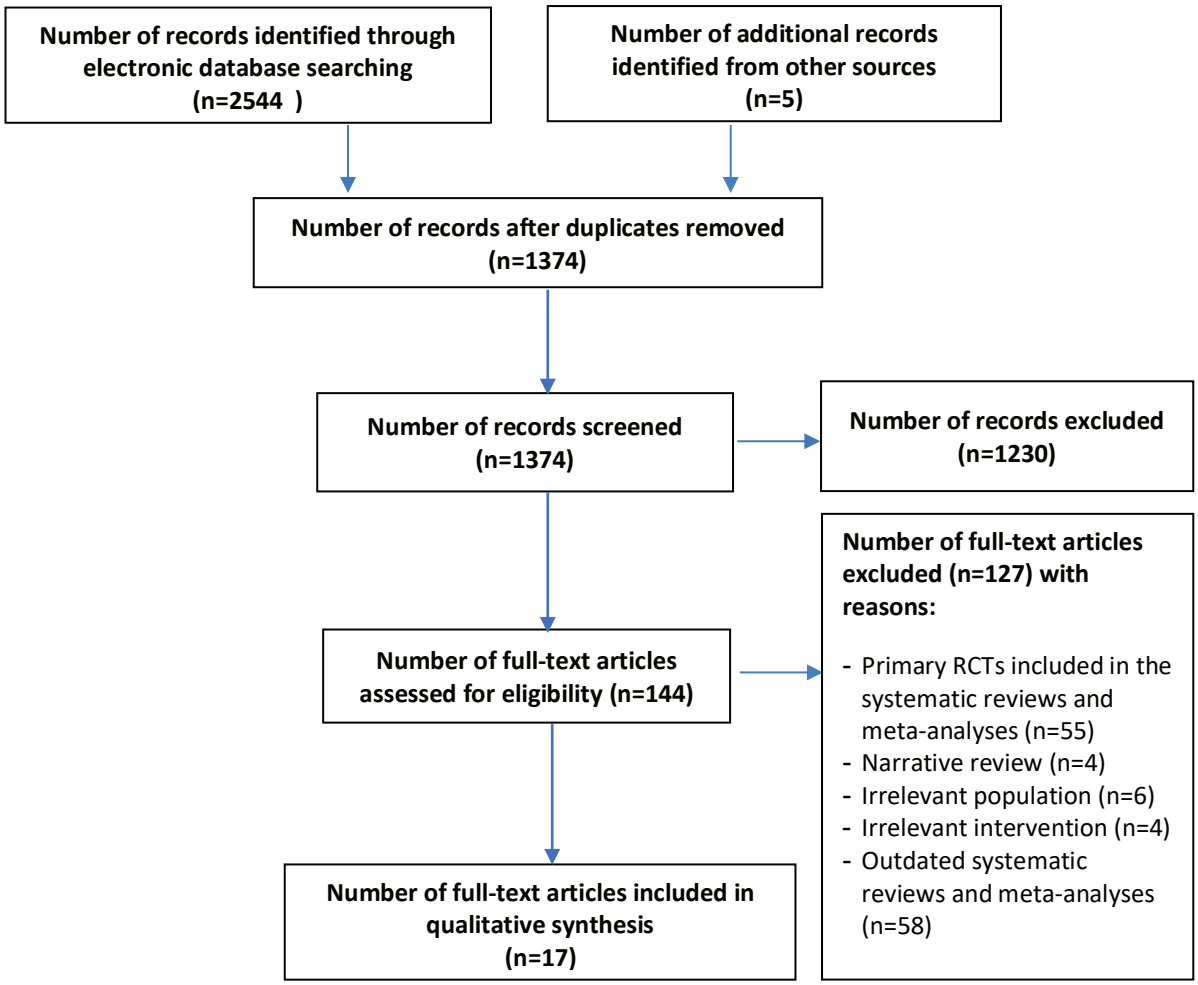


Figure 3 : Flow chart of study selection process

5.2.2 Assessment of risk of bias in included studies

Risk of bias of the included studies was assessed using Risk of Bias in Systematic reviews (ROBIS) [38] for systematic review and meta-analyses, and Critical Appraisal Skill Programme (CASP) checklist for economic evaluation studies. These assessments involved answering a pre-specified question of those criteria assessed and assigning a judgement relating to the risk of bias.

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

Fourteen included systematic review and meta-analysis were rated to have an overall low risk of bias. All the studies had pre-specified their clinical question and inclusion criteria for study eligibility. No language restriction was applied in any of the study. The method used to identify and select the studies was clearly described. All studies provided the search terms and the full search strategy used. The inclusion assessment, appraisal and data collection process were reported to have been conducted independently by at least two reviewers. Three studies [39-41] did not provide information on quality assessment or risk of bias assessment. The quantitative synthesis (network meta-analysis) undertaken was considered appropriate. Statistical heterogeneity was addressed accordingly, and sensitivity analyses were used to assess the robustness the findings. (Table 4)

Table 4: Summary of risk of bias assessment for systematic review and meta-analysis using ROBIS

REVIEW	CRITERIA ASSESSED				
	D1	D2	D3	D4	OVERALL
Siciliano MA et al. (2022) [42]	+	+	+	+	+
He M et al. (2022) [43]	+	+	+	+	+
Fukuda N et al. (2021) [44]	+	+	+	+	+
Fukuda N et al. (2022) [45]	+	+	+	+	+
Zhang X et al. (2022) [46]	+	+	+	+	+
Passiglia F et al. (2018) [47]	+	+	+	+	+
Juarez-Garcia A et al.(2022) [39]	+	+	-	+	+
Pala L et al. (2022) [48]	+	+	+	+	+

REVIEW	CRITERIA ASSESSED				
	D1	D2	D3	D4	OVERALL
Wang Y et al. (2019) [40]	+	+	-	+	+
Zhou C et al. (2022) [49]	+	+	+	+	+
Chen CY et al. (2022) [41]	+	+	-	+	+
Zhang W et al. (2021) [50]	+	+	+	+	+
Yu X et al. (2021) [51]	+	+	+	+	+
Li N et al. (2020) [52]	+	+	+	+	+

Domains
D1: Study eligibility
D2: Identification and selection of studies
D3: Data collection and study appraisal
D4: Synthesis and findings

Judgement
X High risk
- Unclear
+ Low risk

Risk of bias assessment for included economic evaluation studies

Three included economic evaluation studies were rated to have overall low risk of bias. All studies clearly described their research question, interventions of interest and the effectiveness. Reasons for their selected decision-analytic model were given and heterogeneity was reported. All studies clearly described describe how the authors were funded. (Table 5)

Table 5: Summary of quality assessment for economic evaluation studies

REVIEW	CRITERIA ASSESSED									
	D1	D2	D3	D4	D5	D6	D7	D8	D9	OVERALL
Barbier MC et al. (2021)[53]	+	+	+	+	+	+	+	+	+	+
Peng Y et al. (2021)[54]	+	+	+	+	+	+	+	+	+	+
Leung JH et al. (2022)[55]	+	+	+	+	+	+	+	+	+	+

Domains
D1: A well-defined question posed
D2: Comprehensive description of competing alternative given
D3: Effectiveness established
D4: Effects of intervention identified, measured and valued appropriately
D5: All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly
D6: Costs and consequences adjusted for different times at which they occurred (discounting)
D7: Results of the evaluation
D8: Incremental analysis of the consequences and costs of alternatives performed
D9: Sensitivity analysis performed

Judgement
X High risk
- Unclear
+ Low risk

5.2.3 Characteristics of included studies

Fourteen systematic reviews and meta-analysis[39-52] and three economic evaluation studies[53-55] met the inclusion criteria for narrative synthesis. Table 6 provides a summary of the included systematic reviews and meta-analysis characteristics. The reviews were published between 2018 and 2022. Majority of the reviews were 2022 publications. [39, 41-43, 45, 46, 48, 49] Nine reviews undertook network meta-analysis and four reviews undertook conventional meta-analysis. Majority of network meta-analysis were performed using Bayesian approach. Seven reviews evaluated comparative efficacy of ICI based treatments and their toxicity profile (five reviews were conducted in the first line setting and two reviews in second line setting). Majority of reviews included phase III randomized controlled trials (RCTs) in their synthesis. One review evaluated outcomes from the real-world evidence (RWE) in the second line setting.[39] One systematic review generated pooled result of patient reported outcomes (health-related quality of life outcomes) through quantitative synthesis (conventional meta-analysis). [48] Five reviews evaluated the safety profile of ICI based treatments through the conduct of meta-analysis (three Bayesian network meta-analysis[41, 49, 50] and two conventional meta-analysis [40, 51]). One systematic review evaluated the cost-effectiveness of three ICIs (pembrolizumab, atezolizumab, nivolumab) and their chemotherapy combination regimen in both first- and second-line settings. [52] Majority of the reviews did not disclose any specific funding.

Three economic evaluation studies [53-55], published between 2021 and 2022, were included in the evidence synthesis to ensure the completeness of economic evidence presented in the systematic review by Li N et al. [52] Detailed characteristics of the included studies are summarized in Table 7. All included studies represented a full economic evaluation, examining both costs and effectiveness [cost effectiveness analysis (CEA)] from the perspective of Swiss healthcare payer[53], US payer[54] and Taiwan National Health Insurance [55], respectively. Two studies[53, 54] compared cost effectiveness of the treatments in the first-line setting and one study[55] performed the comparison in the second-line setting. All studies developed Markov model and created three similar health states for the analysis with 3-week, 1-month and 3-month cycles, respectively. Two studies[53, 54] applied annual discount rate of 3% and one study[55] applied rate of 3.5% for all costs and

health outcomes. A time horizon of 10 years was chosen by two studies[53, 55] and lifetime by one study[54]. Model outputs included the life-years (LYs)(one study) [54] , quality-adjusted LYs (QALYs) (three studies) [53-55], and incremental cost-effectiveness ratios (ICERs)(three studies) [53-55]. Each study reported different willingness-to-pay (WTP) threshold depending on the country where the analysis was conducted.

Table 6: Characteristics of included systematic reviews

First author	Year of publication	Number of studies included	Population	Intervention and Comparator	Outcomes	Type of meta-analysis performed	Funding
Siciliano MA	2022	19 RCTs - 18 phase III RCTs - 1 phase II RCT	13 599 patients with wild-type (without driver mutation) NSCLC in the first line setting	**Intervention** 17 ICI based regimens **Comparator** Platinum based chemotherapy	1. Comparative efficacy 2. Safety and toxicity	Bayesian network meta-analysis	Italian institutional funds
He M	2022	14 phase III RCTs	3448 patients with advanced NSCLC and high PD-L1 expression in the first line setting **Subpopulation**: NSQ and SQ histology	**Intervention** 11 ICI based regimens **Comparator** Platinum based chemotherapy	1. Comparative efficacy 2. Safety and toxicity	Bayesian network meta-analysis	No specific funding was disclosed
Fukuda N	2021	26 RCTs - 17 phase III RCTs - 9 phase II RCTs	22,619 patients with wild type advanced NSCLC, **non-squamous histology** and **low PD-L1 expression** in the first line setting	**Intervention** 16 ICI based regimens **Comparator** - Platinum based chemotherapy	1. Comparative efficacy 2. Safety and toxicity	Frequentist network meta-analysis	No funding
Fukuda N	2022	48 RCTs - 20 phase III RCTs - 28 phase II RCTs	16 391 patients with wild type advanced NSCLC, **squamous histology** and **low PD-L1 expression** in the first line setting	**Intervention** 11 ICI based regimens **Comparator** Platinum based chemotherapy	1. Comparative efficacy 2. Safety and toxicity	Frequentist network meta-analysis	No specific funding was disclosed
Zhang X	2022	20 RCTS	7,462 patients with wild-type (without driver mutation) NSCLC in the first line setting	16 ICI based regimens	Long term survival outcome - mOS, 1-year and 2-year survival rate	Bayesian network meta-analysis	No specific funding was disclosed
Passiglia F	2018	5 RCTs	Patients with histologically proven diagnosis of NSCLC, who failed prior platinum chemotherapy regimens	**Intervention** 3 ICI monotherapy (pembrolizumab, atezolizumab, nivolumab) **Comparator** Docetaxel	1. Comparative efficacy 2. Safety and toxicity	Network meta-analysis	No specific funding was disclosed

First author	Year of publication	Number of studies included	Population	Intervention and Comparator	Outcomes	Type of meta-analysis performed	Funding
Juarez-Garcia A	2022	66 observational studies	57,016 pre-treated, advanced NSCLC patients	Nivolumab, pembrolizumab and atezolizumab monotherapy	Long term survival outcome - mOS, 1-year and 2-year survival rate	Conventional meta-analysis	Funded by BMS
Pala L	2022	34 RCTs	18,709 patient who received ICI based treatment in first and second-line setting	**Intervention** ICI based regimens **Comparator** standard chemotherapy	Patient-reported outcomes: HRQoL	Conventional meta-analysis	No specific funding was disclosed
Wang Y	2019	125 clinical trials	20,128 patients treated with a single agent PD-1 or PD-L1 inhibitor	**Intervention** PD-1 and PD-L1 inhibitors **Comparator** Standard chemotherapy	Incidences of treatment-related adverse events of PD-1 and PD-L1 inhibitors	Conventional meta-analysis	No specific funding was disclosed
Zhou C	2022	52 RCTs	23,322 patients with NSCLC, receiving ICI based treatment	**Intervention** ICI based regimens **Comparator** Standard chemotherapy	Incidences of serious adverse events; treatment ranking of adverse events	Bayesian network meta-analysis	Funded by China Research Institute and Academic Promotion Program of Shandong First Medical University
Chen CY	2022	21 RCTs - 20 phase III RCTs - 1 phase II RCT	12,626 patients with advanced NSCLC in the first line setting	**Intervention** ICI based regimens **Comparator** Standard chemotherapy	Risk of adverse events with different ICI treatment regimens	Bayesian network meta-analysis	No specific funding was disclosed
Zhang W	2021	12 RCTs - 10 phase III RCTs - 2 phase II RCTs	8,453 patients with NSCLC in first line setting	**Intervention** 6 ICI based regimens **Comparator** Platinum based chemotherapy	1. Incidences of immune-related adverse events for different ICIs-based treatments 2. Safety ranking of immune checkpoint inhibitors (ICIs) for treatment of advanced NSCLC	Bayesian network meta-analysis	No specific funding was disclosed

First author	Year of publication	Number of studies included	Population	Intervention and Comparator	Outcomes	Type of meta-analysis performed	Funding
Yu X	2021	20 RCTs - 16 phase III RCTs - 4 phase II RCTs	13,483 patients with NSCLC	**Intervention** 10 ICI based regimens **Comparator** Standard chemotherapy	1. Incidences of treatment-related fatal adverse events 2. Risk of fatal adverse events with different ICI treatment regimens	Conventional meta-analysis	Funded by The National Natural Science Foundation of China
Li N	2020	21 economic evaluation studies - 16 studies in first line setting - 5 studies in second line setting	Patients with NSCLC	**Intervention** ICI based regimens (pembrolizumab, atezolizumab, nivolumab) **Comparator** Standard chemotherapy	Cost-effectiveness reported as cost per quality-adjusted life years (QALYs) and cost per life year (LY) gained.	Meta-analysis not performed	No specific funding was disclosed

NSCLC = non-small cell lung carcinoma; **RCT** = randomised controlled trial; **ICI** = immune checkpoint inhibitor; **PD-1** = programmed death cell 1;**PD-L1** = programmed death ligand 1; **QALY** = quality - adjusted life year; **LY** = life year; **mOS** = median overall survival

Table 7: Characteristics of included economic evaluation studies

First author	Year of publication	Country	Currency	Perspective	Population	Intervention and Comparator	Type of evaluation	Analysis approach	Time horizon	Annual discount rate	Outcome measure	WTP threshold
Barbier MC	2021	Switzerland	Swiss Franc (year of currency not reported)	Swiss healthcare payer	Patients with advanced NSCLC and high PD-L1 expression, without driver mutation in first line setting	1. Pembrolizumab-chemotherapy combination **vs** 2. Pembrolizumab monotherapy **vs** 3. Platinum based chemotherapy	CEA	3-state Markov cohort simulation model with 1-month cycles	10 years	3%	QALY	CHF100,000
Peng Y	2021	United States	2020 US dollar	US payer perspective	Patients with advanced NSCLC and high PD-L1 expression in first line setting	1. Atezolizumab monotherapy **vs** 2. Platinum based chemotherapy	CEA	3-state Markov cohort simulation with 3-week cycles	lifetime	3%	QALY/LY	US$100,000 to US$150,000
Leung JH	2022	Taiwan	2019 Taiwan dollar	National Health Insurance Administration	Patients with advanced NSCLC in second line setting	3 ICIs (pembrolizumab, atezolizumab and nivolumab monotherapy) compared with docetaxel as a second-line treatment	CEA	3-state Markov cohort simulation with 3-month cycles	10 years	3.5%	QALY	NT$2,221,930 (US$24,408)

WTP = willingness to pay; **QALY** = quality-adjusted life year; **LY** = life year; **CEA** = cost effectiveness analysis

5.2.4 EFFICACY/ EFFECTIVENESS

5.2.4.1 Clinical Efficacy : As First Line Treatment Option

a. Overall Survival (OS)

A systematic review and network meta-analysis was conducted by Siciliano MA et al. in a population of treatment naïve advanced NSCLC patients.[42] The analysis included 19 RCTs involving 13,599 patients and 17 treatment regimens. The treatment regimens comprised of five ICI monotherapy, six ICI plus chemotherapy, two dual ICI, one dual ICI plus chemotherapy, one ICI in combination with anti-angiogenesis plus chemotherapy, anti-angiogenesis plus chemotherapy and a standard chemotherapy alone. The pooled result of the overall population, regardless of PD-L1 status, indicated that ICI-based treatment had a reduced risk of death in comparison to standard chemotherapy alone [pooled hazard ratio (HR) 0.78, 95% confidence interval (CI) 0.73 to 0.83, p<0.001]. A subgroup analysis of PD-L1 positive (PD-L1 expression ≥1%) population revealed lower death risk when ICI-based treatment was compared to standard chemotherapy in a high PD-L1 (PD-L1 expression ≥50%) population (pooled HR 0.68, 95%CI 0.62 to 0.74, p < 0.00001) than in a low PD-L1 (PD-L1 expression 1-49%) population (pooled HR 0.85, 95%CI 0.78 to 0.93, p=0.0005).[42]

<u>Ranking of treatment regimens in high PD-L1 population based on OS outcome</u>

Based on the indirect comparison in network meta-analysis, different ICI treatment regimens ranked differently in specific NSCLC cohorts of interest. Siciliano MA et al. reported in high PD-L1 population, atezolizumab monotherapy had 73.8% probability to be better treatment (pooled HR 0.35, 95%CI 0.15 to 0.80), followed by pembrolizumab in combination with chemotherapy (pooled HR 0.38, 95% CrI 0.21 to 0.68, SUCRA = 70.5%).[42] Another network meta-analysis by He M et al. further sub-analyzed the OS outcome in high PD-L1 population according to their histotypes: squamous and non-squamous histology.[43]

i. High PD-L1 expression with squamous histology [43]

Four studies reported the outcome of OS in squamous NSCLC. Atezolizumab in combination with chemotherapy (pooled HR 0.48, 95% CrI 0.29 to 0.80) showed a significant benefit in improving OS compared to chemotherapy. (Figure 4)

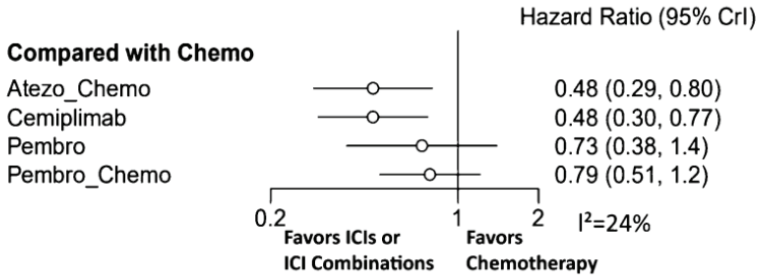


Figure 4: Forest plot of overall survival (OS) for subgroup squamous NSCLC[43]

ii. High PD-L1 expression with non-squamous histology [43]

Five studies reported the outcome of OS in non-squamous NSCLC. Pembrolizumab in combination with chemotherapy (pooled HR 0.42, 95% CrI 0.26 to 0.68), pembrolizumab monotherapy (pooled HR 0.58, 95% CrI 0.41 to 0.83) and cemiplimab monotherapy (pooled HR 0.64, 95% CrI 0.43 to 0.94) showed a better OS than chemotherapy. (Figure 5)

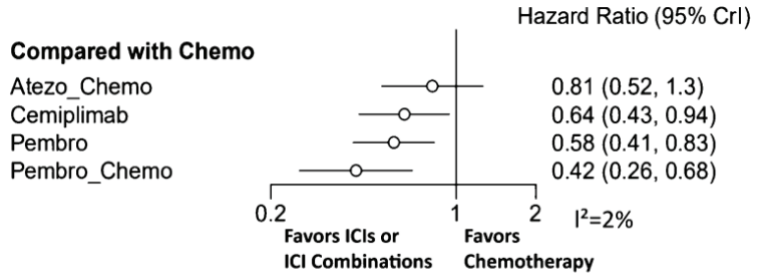


Figure 5: Forest plot of overall survival (OS) for subgroup non-squamous NSCLC[43]

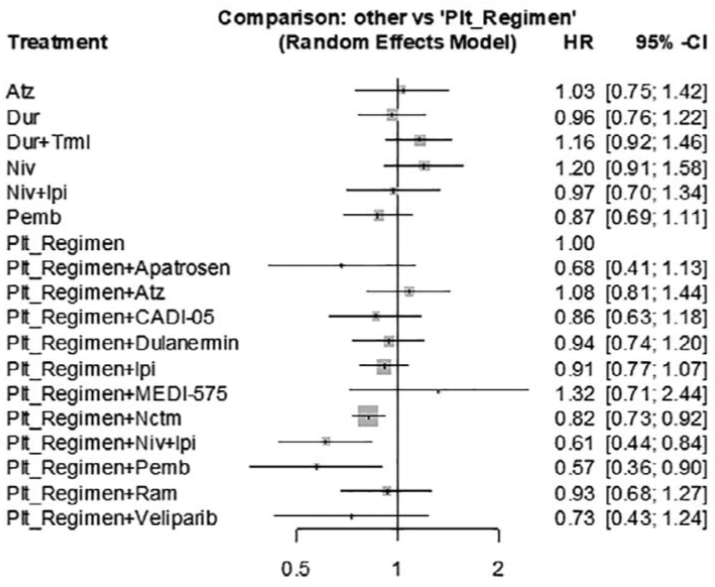
<u>Ranking of treatment regimens in low PD-L1 population based on OS outcome</u>

In low PD-L1 population, pembrolizumab in combination with chemotherapy (pooled HR 0.38, 95% CrI 0.20 to 0.73, SUCRA = 89.3%) and nivolumab in combination with ipilimumab and chemotherapy (pooled HR 0.37, 95% CrI 0.15 to 0.95, SUCRA = 87.7%) reduce the overall death risk as compared to chemotherapy alone. [42] Fukuda N et al.

conducted network meta-analysis for the subgroup of squamous and non-squamous histology.[44, 45]

i. Low PD-L1 expression with squamous histology [45]

Nineteen studies involving 6785 patients were included in the analysis. Pembrolizumab in combination with chemotherapy yielded the best OS benefit compared to chemotherapy alone (pooled HR 0.57, 95% CI 0.36 to 0.90, p=0.016), followed by nivolumab in combination with ipilimumab and chemotherapy (pooled HR 0.61, 95% CI 0.44 to 0.84, p=0.003). (Figure 6)

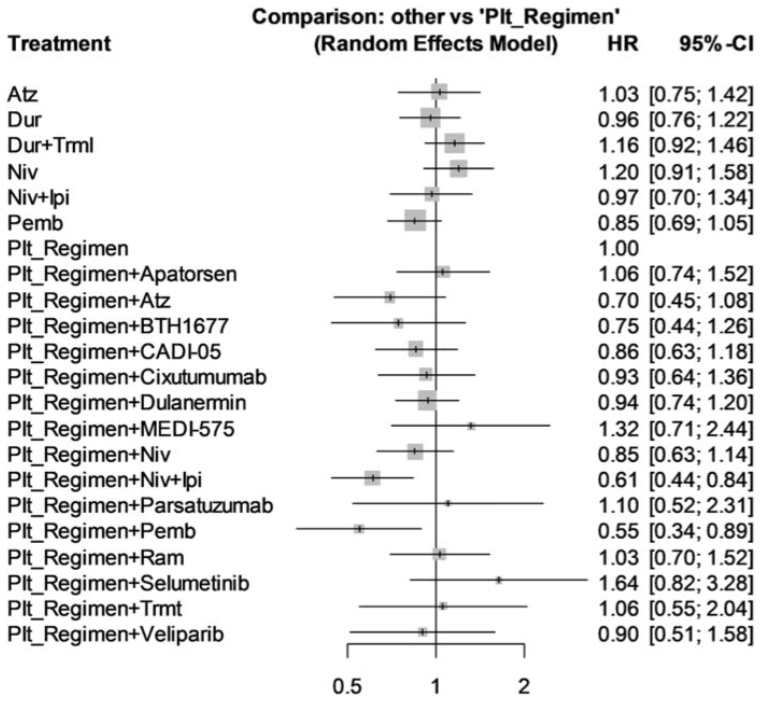


HR, hazard ratio; Plt, platinum regimen; Pemb, pembrolizumab; Niv, nivolumab; Ipi, ipilimumab; Dur, durvalumab; Trml, tremelimumab; Atz, atezolizumab; Trmt, tromethamine; Ram, ramucirumab; Sint, sintilimab; CI, confidence interval.

Figure 6: Forest plot of overall survival (OS) for subgroup squamous NSCLC [45]

ii. Low PD-L1 expression with non-squamous histology [44]

Twenty-six studies with 7,142 patients were included in the analysis. Pembrolizumab in combination with chemotherapy (pooled HR 0.55, 95% CI 0.34 to 0.89, p=0.015) showed the best OS, followed by nivolumab in combination with ipilimumab and chemotherapy (pooled HR 0.61, 95% CI 0.44 to 0.84, p=0.003). (Figure 7)



HR, hazard ratio; Plt, platinum regimen; Pemb, pembrolizumab; Niv, nivolumab; Ipi, ipilimumab; Dur, durvalumab; Trml, tremelimumab; Atz, atezolizumab; Trmt, tromethamine; Ram, ramucirumab; Sint, sintilimab; CI, confidence interval.

Figure 7: Forest plot of overall survival (OS) for subgroup non-squamous NSCLC

b. Progression Free Survival (PFS)

Findings from a network meta-analysis conducted by Siciliano MA et al. in treatment naïve advanced NSCLC population revealed that ICI-based therapy was associated with a reduction of progressive disease (pooled HR 0.69, 95% CI 0.62 to 0.77, p < 0.001). [42] In their review, 14 studies involving 6281 PD-L1 positive patients reported data on PFS. Pooled HR showed a reduction of progressive disease (pooled HR 0.67, 95% CI 0.58 to 0.78, p < 0.00001) in patients receiving ICI-based therapy compared to standard chemotherapy alone. A subgroup analysis of PD-L1 positive (PD-L1 expression ≥1%) population reported lower risk of disease progression when ICI-based treatment was compared with standard chemotherapy alone in a high PD-L1 population (pooled HR 0.58 (95%CI 0.53 to 0.63, p < 0.00001) than in a low PD-L1 population (pooled HR 0.69, 95% CI 0.57 to 0.84, p < 0.00001). [42]

Ranking of treatment regimens in high PD-L1 population based on PFS outcome

According to the SUCRA ranking in the network meta-analysis by Siciliano MA et al., atezolizumab in combination with bevacizumab and chemotherapy was 95.9% likely to be the best regimen in reduction of the risk of disease progression (pooled HR 0.06, 95% CrI 0.01 to 0.23). [42]

i. **High PD-L1 expression with squamous histology** [43]

In systematic review and network meta-analysis conducted by He M et al., four studies reported the outcome of PFS in squamous NSCLC. Atezolizumab in combination with chemotherapy, pembrolizumab in combination with chemotherapy, cemiplimab monotherapy and pembrolizumab monotherapy showed a significant benefit in improving PFS. (Figure 8) Pembrolizumab in combination with chemotherapy was likely to be the best treatment regimen.

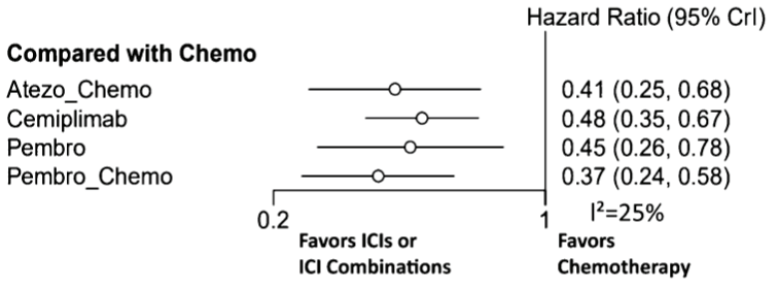


Figure 8: Forest plot of progression free survival (PFS) for subgroup squamous NSCLC [43]

ii. **High PD-L1 expression with non-squamous histology** [43]

In systematic review and network meta-analysis conducted by He M et al., seven studies reported the outcome of PFS in non-squamous NSCLC. Combination of atezolizumab and chemotherapy, pembrolizumab monotherapy and pembrolizumab in combination with chemotherapy showed a significant benefit of improving PFS (Figure 9).

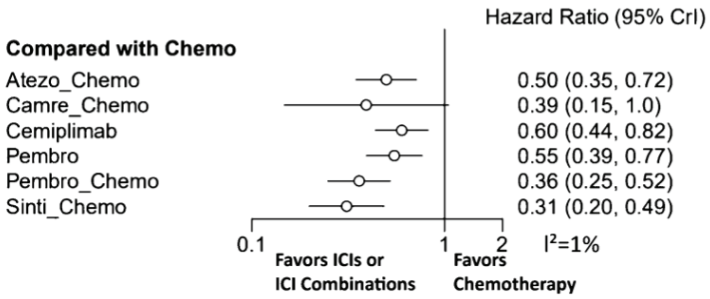


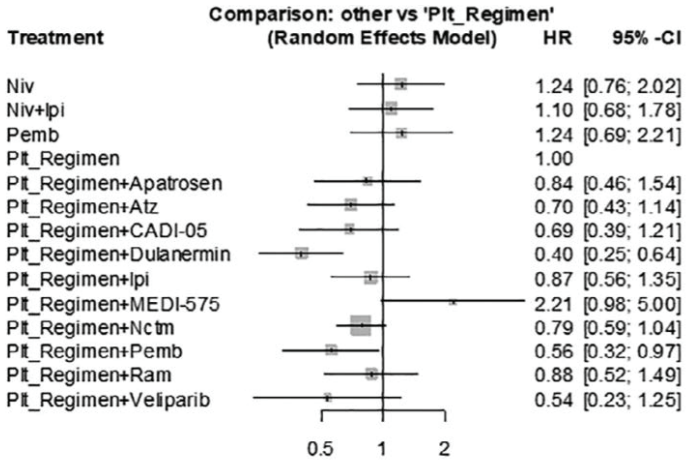
Figure 9: Forest plot of progression free survival (PFS) for subgroup non-squamous NSCLC [43]

Ranking of treatment regimens in low PD-L1 population based on PFS outcome

In low PD-L1 population, network meta-analysis by Siciliano MA et al. showed according to SUCRA rank, atezolizumab plus bevacizumab and chemotherapy was 78.6% likely to be better treatment for PFS (pooled HR 0.37, 95% CrI 0.15 to 0.95), whereas pembrolizumab in combination with chemotherapy ranked second (pooled HR 0.30, 95% CrI 0.12 to 0.72, SUCRA 76%). [42]

i. Low PD-L1 expression with squamous histology [45]

Fukuda N et al. reported pembrolizumab in combination with chemotherapy showed a significantly lower hazard ratio of PFS than chemotherapy alone (pooled HR = 0.56, 95% CI 0.32 to 0.97, p=0.040) and was likely to be the best ICI treatment regimen. (Figure 10)

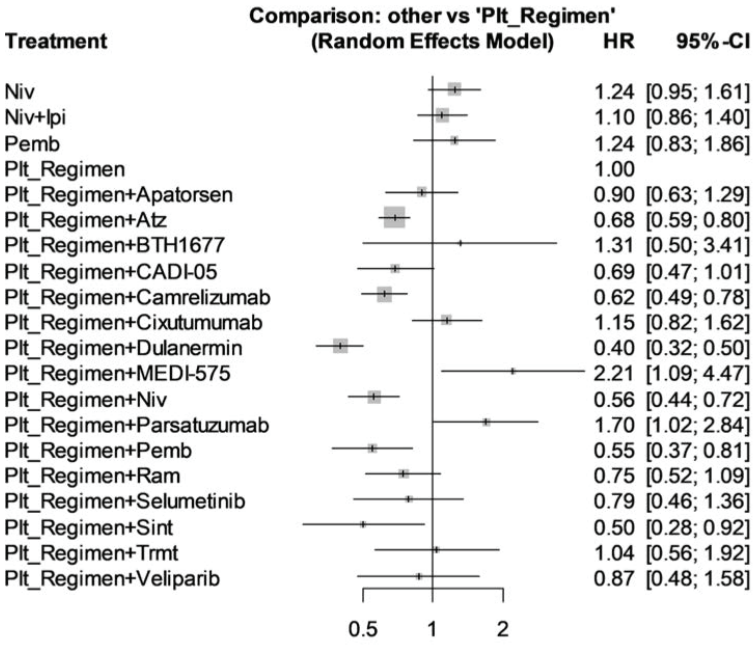


HR, hazard ratio; Plt, platinum regimen; Pemb, pembrolizumab; Niv, nivolumab; Ipi, ipilimumab; Dur, durvalumab; Trml, tremelimumab; Atz, atezolizumab; Trmt, tromethamine; Ram, ramucirumab; Sint, sintilimab; CI, confidence interval.

Figure 10: Forest plot of progression free survival (PFS) for subgroup squamous NSCLC[45]

ii. Low PD-L1 expression with non-squamous histology [44]

Fukuda N et al. reported the pooled PFS had shown that sintilimab in combination with chemotherapy was likely to be the best ICI regimen in reducing of the risk of disease progression, followed by pembrolizumab in combination with chemotherapy and nivolumab in combination with chemotherapy. (Figure 11)



HR, hazard ratio; Plt, platinum regimen; Pemb, pembrolizumab; Niv, nivolumab; Ipi, ipilimumab; Dur, durvalumab; Trml, tremelimumab; Atz, atezolizumab; Trmt, tromethamine; Ram, ramucirumab; Sint, sintilimab; CI, confidence interval.

Figure 11: Forest plot of progression free survival (PFS) for subgroup non-squamous NSCLC[44]

c. Objective Response Rate

Objective response rate (ORR) is defined as proportion of patients with a complete response or partial response to treatment according to Response Evaluation in Solid Tumours (RECIST). As first-line treatment for advanced NSCLC, Siciliano MA et al. reported that ICI-based treatment was associated with a statistically significant higher odds of achieving objective response than standard chemotherapy [pooled odds ratio (OR) 1.69, 95%CI 1.39 to 2.05, p<0.00001]. [42] Atezolizumab-bevacizumab-chemotherapy combination (relative to standard chemotherapy: HR 0.09, 95%CrI 0.02 to 0.84) and pembrolizumab-chemotherapy combination (relative to standard chemotherapy: HR 0.15,

95% CrI 0.08 to 0.51) ranked first and second in the SUCRA ranking profile for ORR. The ICI-chemotherapy combination ranked better than standard chemotherapy. [42] In high PD-L1 population, pembrolizumab-chemotherapy was observed to have highest probability of better response rate (relative to standard chemotherapy: OR 4.2, 95%CI 2.6 to 6.7). Pembrolizumab-chemotherapy showed a significantly superior benefit compared to ICIs monotherapy and nivolumab-ipilimumab combination in the indirect comparison. [42]

d. Long-term survival outcomes

Zhang X et al. conducted a systematic review and network meta-analysis to investigate first line ICI-based treatment that can bring long-term survival to patients with advanced wild-type (without driver mutation) NSCLC.[46] The authors conducted an integrated analysis of the survival outcomes of RCTs on first line ICI-based treatments. Pooled median OS (mOS) was taken as the cutoff value for long-term survival to screen the treatment regimens that can bring long-term survival. A network meta-analysis based on the Bayesian model was performed to compare and rank these treatment regimens with long-term survival according to mOS, 1-year survival rate (1ySR), 2-year survival rate (2ySR), The pooled mOS for ICI-based treatment was 16.2 months (95%CI (95% CI 14.79~17.60) months) with pooled 1-ySR of 63% (95%CI 59%~66%) and pooled 2ySR survival rate of 37% (95%CI 33% to 41%). Among the various treatment strategies, ICI-bevacizumab-chemotherapy combination led to the longest pooled mOS (19.50 months, 95% CI 16.90 to 22.10 months), followed by ICI-chemotherapy combination (16.82 months, 95%CI 14.71 to 18.93 months) and dual ICI-chemotherapy combination (16.07 months, 85%CI 13.84 to 18.29 months). The ICI monotherapy (15.41 months, 95% CI 12.73 to 18.09 months) and dual ICIs (14.08 months, 95%CI 10.00 to 18.15 months) had the shortest pooled mOS. When considering different ICI targets, the anti-PD-1-containing regimens had a longer pooled mOS [18.00 months (95%CI 15.52 to 20.48 months)] than the anti-PD-L1 regimens [17.23 months (95%CI 15.17 to 19.30 months)]. The pooled 1ySR of ICI monotherapy, dual ICI, ICI-chemotherapy combination, dual ICI-chemotherapy and ICI-bevacizumab-chemotherapy were 60% (95%CI 54% to 67%), 55% (95%CI 45% to 65%), 64% (95%CI 0.60 to 0.68), 62% (95%CI 58% to 66%) and 74% (95%CI 67% to 87%), respectively. In term of pooled 2ySR, ICI-bevacizumab-

chemotherapy combination brought the highest survival rate (49%, 95%CI 38% to 61%), while the pooled 2ySR of single ICI, dual ICI, ICI-chemtherapy combination and dual ICI-chemotherapy combination were 38% (95%CI 30% to 46%), 0.35% (95%CI 25% to 45%), 36% (95%CI 30% to 42%) and 33% (95%CI 17% to 49%),-respectively. Based on SUCRA ranking profile, among the treatments that resulted in long-term survival of 16.20 months or more for the all-comer population, pembrolizumab-chemotherapy combination (relative to standard chemotherapy: HR 0.62, 95%CI 0.54 to 0.72) ranked first in mOS, followed by atezolizumab-bevacizumab-chemotherapy (relative to standard chemotherapy: HR 0.71, 95%CI 0.56 to 0.90) and nivolumab-ipilimumab (relative to standard chemotherapy: HR 0.73, 95%CI 0.64~0.84). In terms of median PFS (mPFS), the top three rankings of SUCRA cumulative probability were nivolumab-bevacizumab-chemotherapy (relative to standard chemotherapy: HR 0.31, 95%CI 0.23 to 0.42), atezolizumab-bevacizumab-chemotherapy and pembrolizumab-chemotherapy. In terms of 1ySR, pembrolizumab-chemotherapy combination ranked first, followed by nivolumab-chemotherapy and atezolizumab-bevacizumab-chemotherapy according to SUCRA cumulative probability. The 1ySR of pembrolizumab-chemotherapy was improved significantly compared to atezolizumab-chemotherapy (OR 1.57, 95%CI 1.15 to 2.15) and nivolumab-ipilimumab (OR 1.53, 95%CI 1.10 to 2.12). In terms of 2ySR, the top three cumulative probabilities of SUCRA were atezolizumab-bevacizumab-chemotherapy (versus chemotherapy: OR 1.80, 95%CI 1.29 to 2.52), pembrolizumab-chemotherapy (OR 1.79, 95%CI 1.41 to 2.27), and pembrolizumab (OR 1.67, 95%CI 1.32 to 2.11).

In high PD-L1 population, cemiplimab (HR 0.57, 95%CI 0.42 to 0.77), pembrolizumab-chemotherapy (HR 0.59, 95%CI 0.40 to 0.86) and atezolizumab (HR 0.60, 95%CI 0.40 to 0.89) ranked top three in SUCRA ranking and line chart ranking of mOS. In terms of 1ySR, almost all ICI-related treatments were significantly better than CT, the best of which was pembrolizumab-chemotherapy (versus chemotherapy: HR 2.95, 95%CI 1.62 to 5.44), followed by cemiplimab (versus chemotherapy: HR 2.25, 95%CI 1.59 to 3.21) and nivolumab-ipilimumab-chemotherapy (versus chemotherapy: HR 2.23, 95%CI 1.21 to 4.18). For 2ySR, cemiplimab (relative to chemotherapy: OR 2.75, 95%CI 1.94 to 3.93), atezolizumab (relative to chemotherapy: OR 2.54, 95%CI 1.40 to 4.71) and pembrolizumab (relative to chemotherapy: OR 1.96, 95%CI 1.49 to 2.57) ranked top

three, and almost all ICI-related measures were significantly improved compared to chemotherapy. [46]

5.2.4.2 Clinical Efficacy: As Second and/or Further Lines Treatment Options

Two published network meta-analyses reported comparative efficacy of pembrolizumab, nivolumab and atezolizumab as monotherapy for pre-treated advanced NSCLC population in clinical and real-world settings, respectively. [39, 47]

Passiglia F et al. included five studies in their meta-analysis, comparing clinical efficacy of three ICIs monotherapy (pembrolizumab, nivolumab and atezolizumab).[47] 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 and ORR over docetaxel, atezolizumab monotherapy displayed no significant reduction in disease progression nor improvement in objective response compared to docetaxel. (Table 8) 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. The result also did not show any significant differences in ORR between nivolumab and pembrolizumab monotherapy. However, there were significant higher ORRs in favour of nivolumab and pembrolizumab in comparison to atezolizumab. (Table 9) [47]

Table 8 : OS, PFS and ORR in PD-L1 positive pre-treated patients with advanced NSCLC receiving immune-checkpoint inhibitor versus standard second-line chemotherapy from pairwise comparison [47]

ICI regimen	*versus* Docetaxel		
	OS Pooled HR (95% CI)	**PFS** Pooled HR (95%CI)	**ORR** Pooled OR (95%CI)
Nivolumab monotherapy	0.62 (0.48, 0.81)	0.69 (0.55, 0.87)	2.26 (1.42, 3.61)
Pembrolizumab monotherapy	0.66 (0.57, 0.77)	0.83 (0.74, 0.94)	1.96 (1.48, 2.50)
Atezolizumab monotherapy	0.69 (0.57, 0.85)	0.89 (0.75, 1.06)*	1.09 (0.80, 1.49)*

* Statistically not significant

Table 9: OS, PFS and ORR in PD-L1 positive pre-treated patients with advanced NSCLC receiving immune-checkpoint inhibitor from indirect comparison [47]

Type of comparison	OS Pooled HR (95% CI)	PFS Pooled HR (95%CI)	ORR Pooled OR (95%CI)
Nivolumab *vs.* Pembrolizumab	0.94 (0.69, 1.27)*	0.83 (0.64, 1.08)*	1.15 (0.67, 1.99)*
Nivolumab *vs.* Atezolizumab	0.90 (0.65, 1.25)*	0.77 (0.58, 1.03)*	2.07 (1.18, 3.63)
Pembrolizumab *vs.* Atezolizumab	0.96 (0.75, 1.23)*	0.93 (0.76, 1.15)*	1.80 (1.18, 2.73)

* Statistically not significant

Juarez-Garcia A et al. conducted a systematic review and meta-analysis of existing RWE on the survival outcomes of nivolumab, pembrolizumab and atezolizumab, in second- or higher line in advanced NSCLC. [39] They included 66 cohort studies involving 57,016 pre-treated, advanced NSCLC patients. The studies were mainly from US and Europe countries. Majority of the studies (55 studies - 70%) included a nivolumab-specific study arm. The median OS for nivolumab monotherapy ranged between four to 17 months. The pooled 1- year and 2-year OS rates with nivolumab monotherapy were 45.6% (95% CI 43.4% to 47.8%) and 28.0% (95% CI 24.8% to 31.4%), respectively. The median OS for pembrolizumab monotherapy was 13.5 months and the 1-year OS rate was 53.6% in a PD-L1 positive population. Two-year and 3-year OS rates were not reported for pembrolizumab monotherapy. The reported median OS and 1-year OS rate for atezolizumab monotherapy was 6.5 months and 34.6%, respectively. The 2-year OS rate for atezolizumab was not reached. Subgroup analysis was performed for nivolumab-specific study arms to investigate the predictors of more favourable survival outcomes. Patients with tumours expressing PD-L1 had better median OS and 1-year OS compared to PD-L1 negative patients. Similarly, patients with non-squamous histology had more favourable median OS, 1-year and 2-year OS rates than patients with squamous histology. Fifteen studies compared survival benefit of nivolumab therapy in patients with poor perfomance status (PS) (ECOG > 2) to those with good PS (ECOG ≤ 2). Poor performance status was associated with shorter survival outcomes for nivolumab. Eight studies compared the OS benefit of nivolumab between the elderly (age ≥ 75 years old) versus non-elderly (age < 75 years old) subgroups, and comparable survival outcomes were observed. (Table 10) [19]

Table 10: Association between specific predictor with overall survival outcomes

Predictor	Survival outcomes		
	Median OS	Pooled 1-year OS (%)(95%CI)	Pooled 2-year OS (%)(95%CI)
1. PD-L1 expression status			
PD-L1 positive	8.2–18.1 months	46.3 (34.2– 59.0)	Not calculated (insufficient number of estimates)
PD-L1 negative	5.5 – 9.1 months	27.8 (21.9 – 34.5)	
2. Histology			
Squamous	5.5–15.5 months	41.8 (34.9 – 49.0)	24.7 (18.1 – 32.6)
Non-squamous	5.8–19.3 months	46.6 (43.1 – 50.1)	32.2 (27.0 – 37.9)
3. Perfomance status			
ECOG 1-2	7.3 – 15.5 months	51.6(44.4 – 58.8)	26.4% (21.4 – 32.1)
ECOG >2	2.6 – 7.0 months	27.1(17.8 – 39.0)	Not calculated (insufficient number of estimates)
4. Age			
≥ 75 years old	4.7 – 12.1 months	39.6 (34.8 – 44.6)	21.3 (17.0 – 26.4)
<75 years old	6.3 – 15.5 months	43.2 (39.4 – 47.1)	25.5(19.9 – 32.1)

5.2.4.3 Patient-reported outcomes

Patient-reported outcomes (PROs) are aimed to capture quality of life (QoL) in a comprehensive way from the patient's point of view, taking into account all the different aspects that contribute to its definition. In particular, the time to deterioration (TTD) of PRO score, defined as the time from patient randomization until the first deterioration of PRO score of clinical relevance, is a largely adopted measure to assess treatment effects on patient QoL during the entire trial follow-up, supported by international guidelines.

Pala L et al. conducted a systematic review and meta-analysis to evaluate patient reported outcomes (PROs) assessed in RCTs of ICI-based treatments.[48] Thirty-four RCTs, enrolling a total of 18,709 patients, were included in the analysis. The authors included trials in which PROs were assessed through the Global Health Status (GHS) scale from the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) or the EuroQol Health-Related Quality of Life 5-Dimension, 3-Level (EQ-5D-3L) visual analogue scale (VAS). The GHS scale includes two items that explore the patients' overall health and quality of life. The raw scores are transformed to a linear scale that ranged from 0 to 100. Higher scores on the

GHS scale indicate higher levels of health-related quality of life (HRQoL). The EQ-5D-3L scale evaluates the patient's self-rated health state on a 100-point vertical VAS (with 0 indicating worst imaginable health state and 100 indicating best imaginable health state). The meta-analysis revealed in the group of 19 RCTs testing 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 to 6.4), and the mean change from baseline to 24 weeks of follow-up was 6.1 (95%CI 4.2 to 8.1), significantly favouring PD1/PD-L1 inhibitors. The pooled difference was 1.4 (95%CI −0.4 to 3.2) at week 12 and 2.5 (95%CI −0.8 to 5.9) at week 24 in the group of eight RCTs testing PD1/PD-L1 inhibitors combined with chemotherapy and 2.1 (95%CI −0.8 to 5.0) at week 12 and 2.1 (95%CI −0.4 to 4.5) at week 24 in the group of eight RCTs testing other ICI-containing combinations. The time to deterioration was significantly longer in the immunotherapy-containing groups compared with standard chemotherapy group in all three groups of RCTs evaluated [HRs of 0.80 (95%CI 0.70 to 0.91) for ICIs as monotherapy, 0.89 (95%CI 0.78 to 1.00) for ICIs plus chemotherapy, and 0.78 (95%CI 0.63 to 0.96) for other ICI-containing combinations]. The authors concluded ICIs as monotherapy appear to have a favourable association with patient-reported quality of life and can be combined with other classes of anticancer drugs without worsening this quality of life. [48]

5.2.5 SAFETY

In published literatures, ICI-related adverse events were reported according to the Common Terminology Criteria for Adverse Events (CTCAE), a set of criteria for the standardized classification of adverse effects of drugs used in cancer therapy.[56] It uses a range of grades from 1 to 5. **Grade 1**: is defined as mild, asymptomatic symptoms. clinical or diagnostic observations only; intervention not indicated. **Grade 2**: is moderate; minimal, local or non-invasive intervention was needed. **Grade 3**: severe symptoms or medically significant but not life-threatening but may be disabling or limit self-care in assisted daily living (ADL) **Grade 4**: is life threatening consequences; urgent or emergent intervention needed **Grade 5**: death related to or due to adverse event.[56]

5.2.5.1 Treatment-related adverse events

The pooled result from meta-analysis conducted by Wang Y et al. revealed 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%). [40] Another meta-analysis by Zhou C et al. further reported the pooled incidence of serious adverse for the individual PD-1/PD-L1 inhibitor and combination regimens with chemotherapy. [49] The pooled incidence of serious adverse events for PD-1 inhibitor, PD-L1 inhibitor, PD1-chemotherapy combination, PD-L1-chemotherapy combination and chemotherapy alone were 33.0% (95%CI 27.0% to 40.0%), 37.0% (95%CI 37.0% to 41.0%), 43.0% (95%CI 33.0% to 53.0%), 47.0% (95%CI, 44.0% to 50.0%) and 37.0% (95%CI 34.0% to 40.0%), respectively. [49]

The most common all-grade adverse events were fatigue (18.26%, 95%CI 16.49 to 20.11), pruritus (10.61%, 95%CI 9.46% to 11.83%) and diarrhoea (9.47%, 95%CI 8.43% to 10.58%). The most common serious adverse events were fatigue (0.89%, 95%CI 0.69% to 1.14%), anaemia (0.78%, 95%CI 0.59% to 1.02%) and aspartate aminotransferase (AST) increased (0.75%, 95%CI 0.56% to 0.99%). (Table 11) [40]

Table 11: Pooled incidences of common all-grade adverse events and serious adverse events of PD-1 and PD-L1 inhibitors [40]

All-grade adverse event		Grade 3 or higher adverse event	
Event	**Pooled incidence (%) (95% CI)**	**Event**	**Pooled incidence (%) (95%CI)**
Fatigue	18.26 (16.49 – 20.11)	Fatigue	0.89 (0.69 – 1.14)
Pruritus	10.61 (9.46 – 11.83)	Anaemia	0.78 (0.59 – 1.02)
Diarrhoea	9.47 (8.43 – 10.58)	AST increased	0.75 (0.56 – 0.99)
Rash	9.31 (8.29 – 10.41)	Lipase increased	0.71 (0.51 – 0.98)
Nausea	8.39 (7.40 – 9.39)	ALT increased	0.70 (0.52 – 0.93)
Decreased appetite	7.18 (6.36 - 8.05)	Pneumonitis	0.67 (0.50 – 0.89)
Hypothyroidism	6.07 (5.35 – 6.85)	Diarrhoea	0.59 (0.45 – 0.77)
Arthralgia	5.83 (5.15 – 6.59)	Colitis	0.47 (0.34 - 0.65)
Asthenia	5.58 (4.92 – 6.31)	GGT increased	0.47 (0.30 - 0.69)
Pyrexia	4.77 (4.18 – 5.42)	Hepatitis	0.43 (0.30 – 0.62)
Cough	4.17 (3.64 – 4.77)	Dyspnea	0.42 (0.30 – 0.62)
Dyspnea	3.88 (3.38 – 4.45)	Lymphopenia	0.40 (0.26 - 0.60)
Aneamia	3.84 (3.35 – 4.38)	Hyponatreamia	0.39 (0.25 – 0.59)
Infusion-related reaction	3.63 (3.15 – 4.17)	Asthenia	0.34 (0.25 – 0.48)
Constipation	3.60 (3.12 – 4.13)	Amylase increased	0.30 (0.17 – 0.47)

Additionally, a network meta-analysis of different ICI-based treatment regimens (ICI monotherapy, dual ICI, ICI-chemotherapy, dual ICI-chemotherapy) and chemotherapy alone by Chen CY et al. found ICI in combination with chemotherapy (ICI-chemotherapy) compared to chemotherapy alone carried a significantly higher risk of any treatment related adverse events (TRAEs) [relative risk (RR) 1.99, 95% CrI 1.34 to 2.99].[41] 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). (Figure 10) The ranking profiles for different regimens on the risk of all-grade adverse events and serious adverse events showed that ICI-chemotherapy combinations were associated with the greatest risk, followed by dual ICI-chemotherapy combination, chemotherapy alone, dual ICI and ICI monotherapy, respectively. [41]

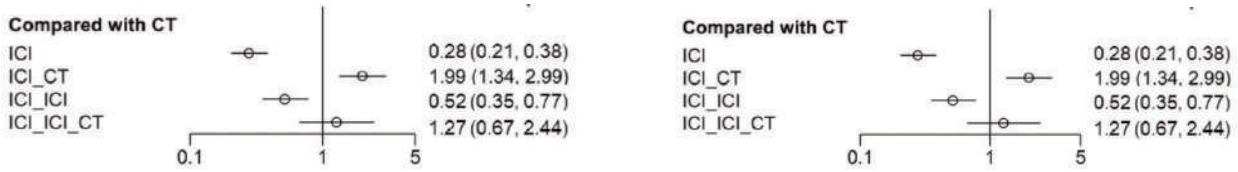


Figure 10: Forest plots of (A) all-grade TRAEs and (B) grade 3 or higher TRAEs for different treatment regimens compared with CT alone [41]

In the review by Siciliano MA et al., the network meta-analysis generated the safety and efficacy ranking profile for the individual regimen in the first line setting for the treatment of advanced NSCLC, showing the probability of each regimen to be better treatment. (Figure 11) [42] 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. Despite ranked as one of the treatments with poor safety profile (SUCRA = 41.5%), average SUCRA value for safety and efficacy outcomes ranked pembrolizumab-chemotherapy combination to have the highest probability to be better treatment in the first line setting (SUCRA = 71.5%). [42]

Treatment	OS	PFS	SAFETY	ORR	Average	Ranking
Pembro + CT	0.780	0.835	0.415	0.829	0.715	1
Cemi	0.710	0.708	0.705	0.715	0.710	2
Tisle + CT	0.709	0.751	0.319	0.803	0.646	3
Pembro	0.683	0.497	0.871	0.440	0.623	4
Atezo + beva + CT	0.412	0.816	0.238	0.919	0.596	5
Nivo + CT	0.554	0.653	0.230	0.801	0.560	6
Camre + CT	0.645	0.687	0.108	0.789	0.557	7
Nivo + ipi + CT	0.660	0.584	0.292	0.615	0.538	8
Nivo + ipi	0.604	0.390	0.592	0.400	0.497	9
Atezo	0.530	0.444	0.818	0.176	0.492	10
Durva	0.392	0.323	0.926	0.192	0.458	11
Atezo + CT	0.234	0.629	0.381	0.583	0.457	12
Beva + CT	0.162	0.520	0.357	0.560	0.400	13
Nivo	0.277	0.097	0.990	0.069	0.358	14
Durva + treme	0.405	0.078	0.689	0.165	0.334	15
CT	0.311	0.170	0.546	0.241	0.317	16
ipi + CT	0.435	0.322	0.093	0.185	0.259	17

Worst — Better

*atezo, atezolizumab; beva, bevacizumab; camre, camrelizumab; cemi, cemiplimab; CT, chemotherapy; durva, durvalumab; ipi, ipilimumab; nivo, nivolumab; NMA, network meta-analysis; ORR, overall response rate; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; SUCRA, surface under the cumulative ranking curve; tisle, tislelizumab; treme, tremelimumab.

Figure 11: Ranking of treatments based on NMA. The SUCRA values for each regimen with regard to PFS, OS, ORR and serious adverse events (G3 or higher).

5.2.5.2 Immune-related adverse events

Pembrolizumab, atezolizumab and nivolumab work by blocking the PD-1 or PD-L1 immune checkpoint pathway to reactivate T cell–mediated anti-tumor immunity. The reactivation of cellular immunity by these checkpoint inhibitors have been reported to cause autoimmune-like disorders.[57] Commonly recognized immune-related adverse events (irAEs) include various endocrine dysfunctions and other autoimmune-like disorders. Among the endocrine dysfunctions, the most frequent all-grade adverse events were hypothyroidism (6.07%, 95%CI 5.35% to 6.85%) and hyperthyroidism (2.82%, 95%CI 2.40% to 3.29%), followed by hyperglycaemia (1.20%, 95%CI 0.91% to 1.55%), thyroiditis (0.75%, 95%CI 0.52% to 1.04%) and adrenal insufficiency (0.69%, 95%CI 0.50% to 0.93%). The most common other all-grade irAEs were diarrhoea (9.47%, 95% CI 8.43% to 10.58%), AST increase (3.39%, 95%CI 2.94% to 3.89%), vitiligo (3.26%, 95%

CI 2.80% to 3.79%), alanine aminotransferase (ALT) increased (3.14%, 95%CI 2.71% to 3.62%), pneumonitis (2.79%, 95%CI 2.39% to 3.23%) and colitis (1.24%, 95%CI 0.99% to 1.54%).[40] For serious irAEs, AST increased (0.75%, 95%CI 0.56% to 0.99%) was most common, followed by ALT increased (0.70%, 95%CI 0.52% to 0.93%), pneumonitis (0.67%, 95%CI, 0.50% to 0.89%), diarrhoea (0.59%, 95%CI 0.45 to 0.77%) and colitis (0.47%, 95%CI 0.34% to 0.65%) (Table 12). Incidences of autoimmune pneumonitis, colitis, and hepatitis are clinically significant.[40]

Table 12: Pooled incidences of the most common all-grade irAEs and the most common serious irAEs of PD-1 and PD-L1 inhibitors [40]

All-grade adverse event		Grade 3 or higher adverse event	
Event	**Pooled incidence (%) (95% CI)**	**Event**	**Pooled incidence (%) (95%CI)**
Endocrine dysfunction		**Endocrine dysfunction**	
Hypothyroidism	6.07 (5.35-6.85)	Hyperglycaemia	0.24 (0.13-0.38)
Hyperthyroidism	2.82 (2.40-3.29)	Adrenal insufficiency	0.18 (0.10-0.30)
Hyperglycaemia	1.20 (0.91-1.55)	Type 1 diabetes	0.18 (0.10-0.30)
Thyroiditis	0.75 (0.52-1.04)	Hypohysitis	0.16 (0.09-0.27)
Adrenal insufficiency	0.69 (0.50-0.93)	Hypothyroidism	0.08 (0.04-0.13)
Hypophysitis	0.60 (0.42-0.82)	Hypothyroidism	0.07 (0.04-0.13)
Type 1 diabetes	0.43 (0.27-0.65)	Thyroiditis	0.04 (0.01-0.10)
Hypopituitarism	0.26 (0.12-0.50)	Hyperthyroidism	0.04 (0.02-0.10)
Other disorder		**Other disorder**	
Diarrhoea	9.47 (8.43-10.58)	AST increased	0.75 (0.56-0.99)
AST increased	3.39 (2.94-3.89)	ALT increased	0.70 (0.52-0.93)
Vitiligo	3.26 (2.80-3.79)	Pneumonitis	0.67 (0.50-0.89)
ALT increased	3.14 (2.71-3.62)	Diarrhoea	0.59 (0.45-0.77)
Pneumonitis	2.79 (2.39-3.23)	Colitis	0.47 (0.34-0.65)
Colitis	1.24 (0.99-1.54)	Hepatitis	0.43 (0.30-0.62)
Bilirubin increased	1.05 (0.75-1.41)	Bilirubin increased	0.15 (0.07-0.28)
Hepatitis	0.85 (0.64-1.10)	Uveitis	0.02 (0.00-0.07)
Uveitis	0.29 (0.15-0.51)	Vitiligo	0.02 (0.00-0.06)

A network meta-analysis by Zhang W et al. demonstrated irAEs toxicity profile and safety ranking of immune checkpoint inhibitors (ICIs) for treatment of advanced NSCLC as shown in Table 10. [50] The irAEs were grouped into target organ or system disorders: endocrine irAEs (hypothyroidism and hyperthyroidism), dermatologic irAEs (rash, pruritus), colitis, pneumonitis and hepatitis (increased AST or ALT). The ICI-based treatments showed a higher risk of irAEs than standard first-line chemotherapy. Higher risk of endocrine and dermatologic irAEs were seen with nivolumab-ipilimumab combination therapy, while higher risk of colitis was seen with atezolizumab-

chemotherapy combination. Pembrolizumab monotherapy had higher risk for pneumonitis and hepatitis. (Table 13) [50]

Table 13: Pooled estimates and SUCRA ranking of treatment regimens for immune-related adverse events according to system or organ disorders [50]

Treatment regimen	Pooled RR (95% CI) *(versus platinum-based chemotherapy)*	SUCRA value
Endocrine		
Nivolumab-ipilimumab	14.43 (1.89–110.2)	79.1%
Durvalumab	10.58 (2.03–55.18)	69.1%
Pembrolizumab	8.26 (2.85–23.97)	61.9%
Atezolizumab-chemotherapy	7.93 (2.78–22.63)	60.4%
Nivolumab	5.77 (1.28–25.98)	45.7%
Pembrolizumab-chemotherapy	4.22 (1.76–10.14)	33.5%
Chemotherapy		0.3%
Dermatology		
Nivolumab-ipilimumab	6.20 (3.23–11.88)	97.4%
Pembrolizumab	3.80 (2.03–7.10)	80.1%
Nivolumab	2.91 (1.74–4.86)	67.1%
Pembrolizumab-chemotherapy	1.95 (1.24–3.06)	43.3%
Atezolizumab-chemotherapy	1.85 (1.21–2.82)	39.9%
Durvalumab	1.23 (0.62–2.42)	17.5%
Chemotherapy		4.7%
Colitis		
Atezolizumab-chemotherapy	8.59 (1.61–45.85)	77.1%
Nivolumab	6.97 (0.36–135.67)	67.3%
Pembrolizumab	4.65 (1.17–18.54)	60.7%
Durvalumab	2.87 (0.12–70.68)	45.2%
Pembrolizumab-chemotherapy	2.59 (0.89–7.51)	41.4%
Chemotherapy		8.5%
Pneumonitis		
Pembrolizumab	22.06 (3.71–131.10)	99.3%
Pembrolizumab-chemotherapy	3.62 (0.76–17.24)	65.1%
Durvalumab	3.48 (0.60–20.28)	62.2%
Atezolizumab-chemotherapy	2.84 (0.66–12.26)	56.0%
Nivolumab	1.83 (0.33–10.28)	35.9%
Chemotherapy		18.1%
Atezolizumab	1.34 (0.39–4.65)	13.3%
Hepatitis		
Pembrolizumab	8.26 (0.98, 69.47)	71.2%
Pembrolizumab-chemotherapy	6.10 (1.08–34.41)	64.3%
Durvalumab	4.80 (0.23–100.25)	56.4%
Atezolizumab-chemotherapy	4.13 (0.89–19.15)	53.8%
Nivolumab	2.97 (0.12–73.14)	44.5%
Chemotherapy		9.8%

5.2.5.3 Treatment-related deaths

Fatal adverse events (FAEs) of ICIs are relatively uncommon. Based on the results of their meta-analysis, Yu X et al. reported the pooled overall incidence of FAEs among all patients diagnosed with NSCLC in the reviewed studies was 1.12% (95% CI 0.83 to1.45, I^2 = 57.40%). 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) (Table 14). [51] The authors also calculated the respective contribution of ICI monotherapy and combination therapy to the FAEs as compared to chemotherapy. The PD-1/PD-L1 monotherapy was significantly associated with lower risk of FAE occurrence (RR = 0.55, 95% CI 0.37 to 0.83, p= 0.004). In contrast, the combined therapy of PD-1/PD-L1 plus chemotherapy significantly higher risk of FAEs (RR 1.76, 95%CI 1.04 to 3.01, p=0.037) compared to standard chemotherapy. The cases of FAEs in infectious diseases and respiratory system disorders accounted for most of the deaths among the patients from the ICI monotherapy and the ICI-chemotherapy group. In comparison to chemotherapy, ICI monotherapy was associated with lower risk of FAEs caused by blood system disorders (RR 0.23, 95%CI 0.07 to 0.73, p= 0.013) and infectious diseases (RR = 0.29, 95% CI = 0.13–0.63, P = 0.002). However, no statistical differences were found in other systems (Table 15). While fatal events in chemotherapy were mainly derived from myelosuppression and infection, in immunotherapy, FAEs were mainly caused by non-infectious pneumonitis, which might result from the overactivation of immune system (Figure 12). ICI combination therapy group reported higher rate of pneumonitis compared to monotherapy and higher rate was also observed with the application of PD-1 inhibitor compared to PD-L1 inhibitor. [51]

Table 14: Pooled incidence of treatment-related fatal adverse events according to treatment regimen for NSCLC patients (20 included RCTs) [51]

Treatment regimens	No. of FAEs	Sample size	Pooled incidence, %	95% CI	I^2
ICI	38	4,577	0.65	0.31–1.07	50.2%
Chemotherapy	81	5,797	1.17	0.74–1.69	56.3%
ICI + ICI	14	947	1.47	0.78–2.36	0.00%
ICI + chemotherapy	48	2,162	2.01	1.42–2.69	5.9%
Overall	181	13,483	1.12	0.83–1.45	57.40%

Table 15: Incidence and risk of system-specific FAE in ICI and chemotherapy [51]

System-specific FAE	Incidence (%)		RR (95%CI)	p-value
	ICI	Chemotherapy		
Monotherapy				
Infections and infestations	0.16	0.73	0.29 (0.13-0.63)	0.002
Respiratory system disorders	0.49	0.40	1.17 (0.59–2.34)	0.656
Blood and lymphatic system disorders	0.00	0.39	0.23 (0.07-0.73)	0.013
Cardiac disorders	0.23	0.25	0.89 (0.29–2.72)	0.834
Metabolism and nutrition disorders	0.00	0.23	0.25 (0.04–1.54)	0.136
Renal and urinary disorders	0.25	0.27	0.93 (0.06-14.79)	0.958
Nervous system disorders	0.15	0.08	1.35 (0.26-6.89)	0.718
Vascular disorders	0.10	0.13	0.70 (0.12-4.10)	0.693
Gastrointestinal disorders	0.16	0	2.90 (0.12–71.08)	0.514
Hepatobiliary	-	-	-	-
Death not otherwise specified	0.23	0.24	0.96 (0.26–3.51)	0.947
Combination therapy				
Infections and infestations	0.53	0.67	0.86 (0.37-2.02)	0.734
Respiratory system disorders	0.91	0.46	1.99 (0.75-5.26)	0.165
Gastrointestinal disorders	0.25	0.51	0.50 (0.05-5.51)	0.572
Nervous system disorders	0.25	0.25	1.00 (0.06-15.97)	0.999
Renal and urinary disorders	0.00	0.36	0.34 (0.01-8.21)	0.503
Cardiac disorders	0.46	0.12	1.99 (0.44-9.09)	0.374
Blood and lymphatic system disorders	0.54	0.16	2.27 (0.51-10.17)	0.283
Hepatobiliary	0.28	0.00	2.39 (0.39-14.79)	0.348
Vascular disorders	0.35	0.00	3.10 (0.32-29.67)	0.327
Metabolism and nutrition disorders	-	-	-	-
Death not otherwise specified	0.40	0.00	2.99 (0.36-24.78)	0.309

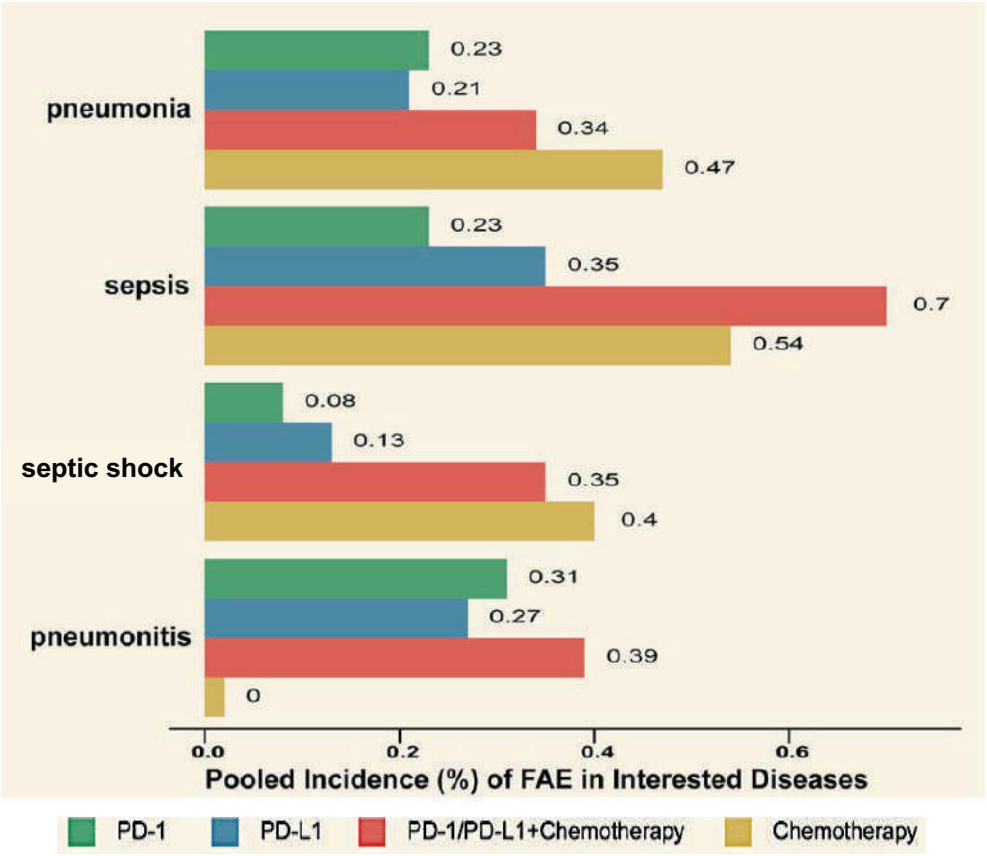


Figure 12: Pooled incidence of FAEs associated with ICI-based treatment and chemotherapy according to specific disorders [51]

5.2.6 COST AND COST-EFFECTIVENESS

There were four included studies on the cost-effectiveness, comprising of one systematic review and three economic evaluation studies.

A systematic review of cost-effectiveness analysis studies was conducted by Li N et al. and 21 studies, published between 2016 and 2019 were included.[52] Comparative regimens consisted of either immune checkpoint inhibitor monotherapy, immune checkpoint inhibitor plus chemotherapy, or chemotherapy alone. Fourteen, four and three studies were about pembrolizumab, nivolumab, and atezolizumab, respectively. The methods mostly used in these studies were Markov and partitioned-survival modelling and sensitivity analysis. All studies used quality-adjusted life year (QALY) and life year (LY)

as outcomes. Most studies were conducted in high-income countries (17 studies). Of the 14 pembrolizumab studies, 13 studies investigated pembrolizumab as first-line treatment. Of the 13 studies, eight showed that pembrolizumab was more cost-effective 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 biomarker-identified advanced NSCLC. 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 WTP thresholds (US: $100,000; UK: $42,048) as the ICER values of both countries were close to each other in nearly all sensitivity and dependency analyses. Nivolumab was used for second-line treatment in the included studies. Four studies on nivolumab did not clearly demonstrate this drug to be cost-effective. One study showed that a trade-off between improving patient survival and QALYs and increasing costs exist regardless of the cost-effectiveness of nivolumab. Three other nivolumab studies showed that the drug was not cost-effective at the current national threshold but could be improved by PD-L1 testing or special funding methods. 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. Another two studies concluded that the combination of atezolizumab-bevacizumab-carboplatin-paclitaxel was less cost-effective than that of bevacizumab-carboplatin-paclitaxel or carboplatin-paclitaxel in the first-line treatment of patients with NSCLC.[52]

Barbier MC et al. conducted a cost-effectiveness analysis for Switzerland comparing pembrolizumab monotherapy [at a fixed dose of 200 mg intravenously (IV) every 3 weeks] or in combination with chemotherapy, the two new treatment options for patients with metastatic non-squamous non-small cell lung cancer (NSCLC) and high (⩾ 50%) PD-L1 expression.[53] A 3-state Markov model with time horizon of 10 years was constructed. Parametric functions were fitted to Kaplan–Meier OS and PFS using 2-year follow-up data from the KN-024 and KN-189 registration trials. The cost estimation for further treatment lines and costs for best supportive care was made by authors. Costs were assessed from the Swiss healthcare payer perspective with WTP of CHF 100,000 (approx. MYR

470,000). Published utility values was used. Combination therapy resulted in an expected gain of 0.17 quality-adjusted life years (QALYs) per patient and incremental costs of Swiss Francs (CHF) 81,085 as compared to pembrolizumab. These estimates led to an incremental cost-effectiveness ratio (ICER) of CHF 475,299/QALY. Pembrolizumab in comparison to chemotherapy was estimated to generate mean incremental QALYs of 0.83 and incremental costs of CHF 56,585, resulting in an ICER of CHF 68,580/QALY. Results were most sensitive to changes in costs of first line pembrolizumab and combination therapy, together with changes in PFS. In the probabilistic sensitivity analysis, combination therapy was cost-effective in 4.9% of the simulations and pembrolizumab monotherapy in 82.9%, assuming a willingness-to-pay threshold of CHF 100,000 per QALY gained. The authors concluded pembrolizumab was likely to be cost-effective from the Swiss healthcare payer perspective, whereas pembrolizumab plus chemotherapy was not. [53]

Peng Y et al. evaluated the cost-effectiveness of atezolizumab (at fixed dose 1200 mg IV every 3 weeks) as the first-line treatment for NSCLC with high PD-L1 expression from the US payer perspective.[54] A Markov model with three health states was developed to estimate the cost and outcome of atezolizumab versus platinum-based chemotherapy in patients with previously untreated metastatic NSCLC with high PD-L1 expression. Model outputs included the life-years (LYs), QALYs, total cost, and ICERs. Atezolizumab produced an additional 1.32 QALYs (2.08 LYs) compared with platinum-based chemotherapy. The accompanying incremental cost was US$224,590. The results of one-way sensitivity analysis found that the ICER was most sensitive to the HR of OS. The probabilistic sensitivity analysis showed that the probability of atezolizumab being cost-effective compared with platinum-based chemotherapy was 10.28% and 37.71% at the WTP threshold of US$100,000/QALY and US$150,000/QALY, respectively. The authors concluded that atezolizumab was estimated not to be cost-effective compared to platinum-based chemotherapy in the first-line treatment of patients with NSCLC with high PD-L1 expression. [54]

Leung JH et al. evaluated the cost–effectiveness of immune checkpoint inhibitors versus docetaxel in pre-treated patients with advanced non-small-cell lung cancer.[55] The analysis was conducted from the National Health Insurance Administration (NHIA) perspective in Taiwan with WTP threshold of New Taiwan (NT)$2,221,930 [US$24,408 (1US$ = NT$30)] per QALY gained. A Markov model was constructed to simulate the clinical outcomes and costs of advanced non-small-cell lung cancer. Clinical outcomes data were derived from RCTs: Checkmate-017, Checkmate-057 for nivolumab (at a fixed dose of 3 mg/kg IV once every 2 weeks) versus docetaxel, KEYNOTE-010 for pembrolizumab (2 mg/kg or 10 mg/kg every 3 weeks) versus docetaxel and OAK for atezolizumab (at fixed dose of 1200 mg IV every 3 weeks) versus docetaxel. Drug acquisition cost and other health resource use were obtained from the claim data of a tertiary hospital and the National Health Insurance. The outcome was an ICER expressed as cost per QALY gained. Compared with docetaxel, pembrolizumab was associated with increased costs of NT$396,965 and QALYs by 0.954 in NSCLC populations; ICER was NT$416,102/QALY; while nivolumab and atezolizumab were associated with increased costs of NT$689,912 and NT$1,028,653, QALYs increased by 0.439 and 0.651. The resulting ICERs for treating patients with nivolumab and atezolizumab compared with docetaxel were NT$1,572,912/QALY and NT$1,580,469/QALY for NSCLC patients. Thus, the use of pembrolizumab, nivolumab and atezolizumab for treating patients with NSCLC was cost effective compared with docetaxel. When nivolumab monotherapy or atezolizumab monotherapy were compared with pembrolizumab monotherapy, the incremental cost for nivolumab and atezolizumab were NT$292,947 and NT$631,688, respectively; yet, the incremental QALYs for nivolumab and atezolizumab were lower than that of pembrolizumab. Therefore, nivolumab monotherapy and atezolizumab monotherapy were not cost effective compared to pembrolizumab monotherapy. The authors concluded that pembrolizumab monotherapy was more cost effective than nivolumab and atezolizumab compared to docetaxel as a second-line regimen for patients with previously treated advanced NSCLC at willingness to pay threshold in Taiwan.[55]

5.2.7 ORGANISATIONAL

Access to immunotherapy as a high-cost drug

i. Reimbursement policy

Huang LY et al. described the reimbursement policy for immune checkpoint inhibitors in Taiwan.[58] The national health insurance (NHI) coverage with an upper limit of NT$800 million (≈US$26.7 million) is provided for cancer immunotherapy in Taiwan. With the aim to enhance the accessibility of advanced therapy, the Taiwan National Health Insurance Administration announced two pathways for high-cost medicine: the managed entry agreement and a set of general rules of reimbursement submission for high-cost drugs which include a precertification mechanism for reimbursing these new immunotherapy drug. Details such as physical status, PD-L1 status, medical record and treatment protocol were collected. The reimbursement scheme decided that coverage priority should be given to patients with high levels of PD-L1 expression to increase the effectiveness of new drugs. A patient registry system was created to collect real-world data (RWD) from patients using the cancer immune checkpoints, to understand the therapeutic effects of immune-oncologic treatment in Taiwanese patients, thereby enabling payers to adjust payment regulations and scope. The RWD is considered a better representation of local patient demographics as it is more reflective of clinical practice and potentially more closely aligned with contemporary treatment patterns. Reimbursement review according to the RWD is done every three months. Those exhibiting a complete or partial response to the therapy may continue using the drugs, whereas those presenting progressive disease or exhibiting moderate, severe, or life-threatening adverse reactions should immediately cease using ICI. On 1 April 2019, the NHIA covered three ICIs—atezolizumab, pembrolizumab, and nivolumab—for eight diseases and the ten indications. Since then, more than 1,000 patients have been reimbursed for treatment with these immune-oncologic drugs, and the budget has been controlled within the originally set range. The current challenge is expanding indications and combination regimens of these immune-oncologic drugs within the same budget. [58]

ii. Treatment optimization

Treatment optimization with a reduced unit dose, less frequent schedule and/or shorter duration of treatment could be a promising strategy to reduce costs and potentially toxicity, thereby improving access to effective immune-oncologic treatment. In phase 1 studies, ICIs have shown efficacy at lower doses than those approved, with no evidence of a dose–response relationship but showing prolonged bioavailability and target binding.[59] In the Phase I MK-3475 study, pembrolizumab showed full target engagement at doses of 1 mg kg−1 every 3 weeks or higher, and there were no differences in response rates between 2 and 10 mg kg−1.[60] Retrospective data from patients with NSCLC at two tertiary Korean hospitals, treated with low-dose nivolumab (20 or 100 mg fixed dose every 3 weeks) showed similar survival outcomes and response rates to those who received standard dose nivolumab (3mg/kg every 2 weeks).[61] At the time of writing this review, there are 16 ongoing clinical trials to optimize immune checkpoint inhibitors in advanced cancer either with early cessation, extended interval or reducing the dose.(Table 16) [59]

Table 16: The ongoing clinical trials to optimize immune checkpoint inhibitors in advanced cancer [59]

Type	Trial	Indication	Design	Planned *n*	Country	Registration number
Early cessation	DANTE	Melanoma	Randomized between stop at 1 year vs continue to 2 years in responding patients	1,208	UK	ISRCTN15837212
	STOP-GAP	Melanoma	Randomized between stop at response (restart at progression) vs continuous treatment to 2 years	614	Canada	NCT02821013
	SAFE STOP	Melanoma	Stop on complete response, single-arm cohort, PFS at 2 years	200	The Netherlands	NL7293 (NTR7502)
	PET-STOP	Melanoma	Stop on PET-CR, single-arm cohort, PFS	150	USA	NCT04462406
	SAVE	NSCLC	ICI after chemotherapy randomized to stop at 1 year vs continuation	216	Japan	JCOG1701
	STOP	Renal cell carcinoma	ICI responding at 1 year randomized to stop at 1 year vs continuation	216	Japan	JCOG1905
	DIAL	NSCLC	Randomized between 6 months and 2 years of pembrolizumab after chemotherapy	114	France	NCT05255302
	OPTIMICE-pCR	TNBC	Observation vs adjuvant ICI after chemo-immunotherapy combination	1,295	USA	TBC
Extended interval	NCT04295863	Any	1x vs 2x SOC interval	264	USA	NCT04295863
	REFINE	Basket (renal)	MAMS initially 1x vs 2x SOC interval expanding to 3x	160	UK	NCT04913025
	MOIO	Any	SOC vs 12 weeks	656	France	NCT05078047
	REFINE-Lung	NSCLC	MAMS initially pembrolizumab 6 vs 12 weeks	1,750	UK	NCT05085028
	NCT04032418	NSCLC	Pembrolizumab 3 vs 12 weeks after combination chemotherapy	152	USA	NCT04032418
	PULSE	NSCLC	Pembrolizumab 3 vs 6 weeks after combination chemotherapy	1,100	France	TBC
Low dose	NVALT-30 Dedication	NSCLC	Randomized between pembrolizumab and pembrolizumab 25% dose reduction	750	The Netherlands	EudraCT 2020-000493-15
	CTRI-DELLI	HNSCC	Low-dose nivolumab (20 mg twice weekly) vs chemotherapy	TBC	India	CTRI/2020/02/023441

ICI, immune checkpoint inhibitors; MAMS, multi-arm, multi-stage; SOC, standard of care; TBC, to be confirmed.

A local published case series by Wong PY et al., presented three cases of advanced NSCLC with high PD-L1 expression in the absence of EGFR and ALK alterations treated with limited doses of ICI in the first line setting due to financial constraint, showing durable partial response for more than 19 months after treatment cessation. [62] The patients described in these cases were elderly, aged more 80 years old with ECOG 2 and yet they experienced good response (reduction in tumour size and improvement in QoL). Detailed description of the cases is as shown in Table 17. [62]

Table 17: Case description of NSCLC in the first setting line with limited doses/shorter course of ICI treatment [62]

CASE DESCRIPTION	DIAGNOSIS	PD-L1 EXPRESSION	TREATMENT RECEIVED	OUTCOMES
CASE 1: 88-year-old lady, ex-smoker (15 pack years), no EGFR and ALK mutation	Squamous cell carcinoma, stage IIIA NSCLC (T2N2M0)	High – 80%	**Extended interval and early cessation** IV Atezolizumab 1200 mg **First dose**: March 2020 **Second dose**: November 2020 **Third dose**: February 2021 No adverse event reported	**1. Reduction in tumour size** - Initial CT thorax: heterogenous mass measuring 4.4 × 3.8 × 4.2 cm - Repeated CT thorax February 2021: mass size was 2.7 × 2.9 × 2.9 cm **2. Symptoms improvement**
CASE 2: 82-year-old gentleman, smoker (80 pack year), no EGFR and ALK mutation	Stage IV lung adenocarcinoma (T4N3M1b)	High - 95%	**Lower dose** IV Pembrolizumab 100mg **First dose**: November 2019 **Second dose**: 6 weeks later No adverse event reported	**1. Reduction in CEA level** - Initial CEA: 580 ng/ml - Repeated CEA: 106 ng/ml -> 3.0 ng/ml **2. Reduction in tumour size** - Initial CT Thorax: mass size 12.4 × 10.0 × 8.4 cm - Repeated CT Thorax March 2020: tumour reduction with an apical mass thickness measuring 2.0 cm, previously seen lymph nodes had shrunk to subcentimeters. **3. Symptoms improvement**
CASE 3: 87-year-old gentlemen, non-smoker, no EGFR and ALK mutation	Stage IV lung adenocarcinoma (T4N2M1b)	High – 80%	**Early cessation and lower dose** **November 2019**: 2 doses of IV pembrolizumab 100 mg, 3 weekly **October 2020**: 2 more doses of IV pembrolizumab 100 mg, 3 weekly due to disease progression No adverse event reported	**Reduction in tumour size** - Initial CT Thorax: left lower lobe measuring 13.3 × 8.8 cm, encasing the descending aorta and extending to the lower oesophagus. - Repeated CT scan 3 months later: mass size 4.6 × 4.6 × 4.3 cm - **September 2020**: CT scan showed a slightly increased tumor size of 5.6 × 4.1 × 4.6 cm. - Repeated CT scan after another 2 doses of pembrolizumab: a reduced mass measuring 4.8 × 3.7 × 4.0 cm

5.2.8 SOCIAL/ ETHICAL / LEGAL

There was no retrievable evidence on social, ethical and legal aspect of immunotherapy for the treatment of advanced NSCLC.

5.3 DISCUSSION

Presently, immunotherapy plays an important role in the treatment of patients with NSCLC, changing the traditional paradigm of cancer treatment. This review was undertaken to assess the clinical efficacy and health-related outcomes as well as economic implication of locally available immune checkpoint inhibitors namely pembrolizumab, nivolumab and atezolizumab, in the treatment of advanced NSCLC. The evidence to support the introduction of immune checkpoint inhibitors as standard treatment for advanced NSCLC in Malaysia is of high-level evidence with good methodological quality. There are seven most recent systematic review and network meta-analysis included in this review that focus on evaluating the comparative efficacy of these ICIs against standard chemotherapy and various ICI combination regimens in first line and second/subsequent line settings. One systematic review and meta-analysis provided evidence on patient reported outcomes in health-related quality of life of cancer patients receiving ICI-based treatments in clinical trials. Two network meta-analyses and three conventional meta-analysis explored the occurrence of adverse events with ICI based treatments.

Our evidence synthesis had shown that ICI-based treatment alone or in combination was associated with better clinical benefits in terms of OS, PFS and ORR compared to standard chemotherapy for advanced NSCLC. Acceptable safety profile was also observed with these treatments. The spectrum of adverse events of ICIs is different from that of all other systemic therapies, and many patients develop no or mild adverse events that do not substantially affect quality of life. In first line setting, pembrolizumab either as monotherapy or in combination with chemotherapy ranked high in probability of better treatment option among ICI-based treatment, especially in advanced NSCLC population with high PD-L1 expression. While in pretreated population, nivolumab monotherapy ranked best. Despite been efficacious, pembrolizumab-chemotherapy combination

regimen reported worse safety profile, predominantly associated with the occurrence of pneumonitis, immune related adverse event. Improvement in health-related QoL over time favour ICI monotherapy. However, in trials testing ICI-containing combinations, the degree of QoL improvement in favour of ICIs was limited and under the clinically relevant cutoff, which does not allow for the conclusion of better quality of life in patients treated with an ICI combination. Regardless, it may support the conclusion that none of the ICI combinations worsened patient QoL compared to standard chemotherapy treatment. The meaningful efficacy of ICI based treatment allow a significantly longer preservation of quality of life for patients treated with immunotherapy. Nevertheless, the burden of high cost limits the access. Studies on the cost-effectiveness of ICIs for NSCLC reported country specific cost-effectiveness outcomes, whereby generalizability is limited due to different clinical practice patterns, health-care systems, cultural and ethical practices, and willingness to pay thresholds. The treatment most likely to be cost-effective in high-income countries. Innovative approaches of way to improve access continuously been considered. The obvious gap between clinical efficacy of ICIs and their high cost poses a challenge for healthcare system, mainly from resource limited countries, in provision of better treatment.

This review captures a comprehensive set of findings from the most recent publications of systematic review and meta-analysis of ICI based treatment in advanced NSCLC, which ensure the inclusion of latest outcome data from the clinical trials. However, the review has several limitations. Only English full text articles were included in this review. Hence, there is a possibility that potentially relevant studies published in languages other than English could have been missed. The included systematic reviews and meta-analysis synthesized evidence produced by clinical trials that were either fully or partially funded by the manufacturer. Funding could be a source of bias. It could lead to overestimation of benefits or underestimation of harms of ICIs. While RCTs are considered the gold standard of evidence, analysis of their findings may not accurately translate to real-world settings. In view of their pre-specified eligibility criteria, subpopulation of patients may be underrepresented in clinical trials. Future research focusing on RWE may provide valuable context for clinical trial findings, especially in local setting.

6.0 PART B: ECONOMIC EVALUATION

COST-EFFECTIVENESS ANALYSIS

6.1 OBJECTIVES

i. To assess the cost-effectiveness (CE) of PD-1/PD-L1 inhibitors in comparison to chemotherapy in treating advanced metastatic NSCLC patients in Malaysia

ii. To estimate the incremental cost-effectiveness ratio (ICER) of PD-1/PD-L1 inhibitors as first-line and second-line treatment in comparison to chemotherapy for advanced metastatic NSCLC patients in Malaysia

6.2 METHODS

6.2.1 Analytical Overview and Model Structure

A state transition model (Markov cohort simulation) consisting of three mutually exclusive health states: progression-free (PF), progressive disease (PD) and death, with 3-week cycle length and a lifetime horizon was developed using Microsoft Excel 2019. It followed a hypothetical cohort of metastatic advanced stage of NSCLC patients who had positive PD-L1 expression (at least one per cent) treated with a PD-1/PD-L1 inhibitor as a first-line or second-line treatment. The comparator in both treatment settings was conventional chemotherapies available in MOH facilities.[12] In the first-line setting, the interventions compared were pembrolizumab 200mg and atezolizumab 1,200mg, administered intravenously every three weeks either as monotherapy or in combination with platinum-based chemotherapy.

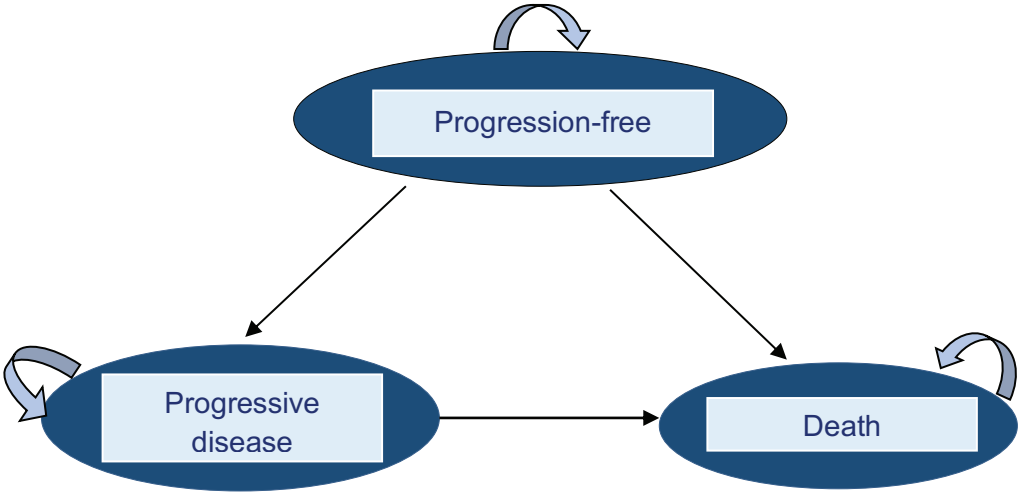


Figure 13: Markov model

Meanwhile, the interventions considered in the second-line setting were intravenous nivolumab administered 3mg/kg every two weeks, pembrolizumab 2mg/kg and atezolizumab 1,200mg, both administered intravenously every three weeks. All simulated patients began at PF state and then would either remain in their current state or redistribute to PD or death states during each Markov cycle state according to time-dependency transition probabilities (**Figure 13**). After disease progression, it was assumed patients were not offered next alternative treatment and would receive best supportive care until death.

The described model was analysed independently in estimating the total costs, quality-adjusted life-years (QALYs) gained and ICER associated with the use of PD-1/L1 inhibitors as first-line or second-line treatment compared to conventional chemotherapy. As there was no explicit national CE/ICER 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).[63] This analysis was conducted from the perspective of MOH and an annual three per cent discount rate was applied to both costs and outcomes.[64]

6.2.2 Clinical Parameters

The published Kaplan-Meier (KM) curves for progression-free survival (PFS) and overall survival (OS) for comparator arms from three clinical trials, KEYNOTE-407 and KEYNOTE-189 (first-line treatment), and KEYNOTE-010 (second-line treatment) were used to inform the baseline transition probabilities for NSCLC patients with tumour proportion score (TPS) of at least one per cent, respectively.[65-67] Fitting of appropriate survival curves to the summary survival data were based on method and spreadsheet template developed by Hoyle and Henley (2011).[68] Firstly, the data points from the PFS and OS curves were extracted using DigitizeIt, a plot digitizer software, to reconstruct these KM curves.[69] A web-based application, Shiny, then was used to reconstruct pseudo-individual patient data and calculate empirical survival probabilities corresponding to the time interval specified in the spreadsheet, utilising the obtained data points earlier.[70]

Four parametric survival distributions (exponential, Weibull, log-normal and log-logistic) were applied to parameterise the curves and extrapolating them over the model time horizon. Log-logistic parametric survival distribution was evaluated to have the best fitting for both PFS and OS curves for the comparator arms of both first- and second-line treatment based on Akaike information criterion (AIC) and visual inspection. Based on the results from Section A of this report, analysis for the first-line treatment was conducted according to the two most common histological subtypes of NSCLC: squamous and non-squamous, and further analysed according to PD-L1 expression level: low to intermediate (tumour proportion score (TPS) between one to 49 per cent) and high (at least 50 per cent). On the other hand, the population considered for the second-line treatment comprised both subtypes with TPS of at least one per cent. The parameters fitting of the chosen survival model were as shown in Table 18.

6.2.3 Transition Probabilities

Time-dependency transition probabilities for the Markov model were calculated using the survival parameters and survival function of each PFS and OS curves obtained in the previous section. The baseline transition probabilities between health states for the comparator arms were based on the formula described in a previously published CE

study.[71] The PFS and OS for the intervention arms were then estimated by multiplying the hazard ratio (HR) of each PD-1/L1 inhibitors reported in Section A of this report and the PFS and OS rates of the comparator arms.

Table 18: Survival model parameters fitting to comparators arms in KEYNOTE-407 and KEYNOTE-189

Populations	PFS		OS	
	Model	Parameter	Model	Parameter
Treatment-naïve squamous NSCLC with positive PD-L1 expression*	Log-logistic	Shape: 1.603 Scale: 0.524	Log-logistic	Shape: 2.53 Scale: 0.774
Treatment-naïve non-squamous NSCLC with positive PD-L1 expression**	Log-logistic	Shape: 1.529 Scale: 0.87	Log-logistic	Shape: 2.48 Scale: 0.568
Previously treated NSCLC with positive PD-L1 expression***	Log-logistic	Shape: 1.490 Scale: 0.585	Log-logistic	Shape: 2.132 Scale: 0.734

** platinum-based chemotherapy in KEYNOTE-407*
*** platinum-based chemotherapy in KEYNOYE-189*
****chemotherapy in KEYNOTE-010*

6.2.4 Cost and Utility Inputs

This analysis only considered direct medical costs which included drug acquisition cost, intravenous drug administration cost, best supportive care cost for those who progressed after being treated with a PD-1/L1 inhibitor, routine follow-up visit cost as well as management cost of serious treatment-related adverse events.

The drug costs were calculated based on the recommended dose for a patient with assumed body weight of 65 kilogram and body surface area (BSA) of 1.73m^2. Despite availability of several chemotherapy regimens for both first- and second-line treatment of advanced metastatic NSCLC in MOH facilities[12], it was assumed in this analysis that they produced similar treatment effect at similar cost. Hence, the average cost of these drugs was used instead.[72] Meanwhile, costs for the PD-1/L1 inhibitors were based on the public facilities procurement costs in year 2020 provided by the Pharmaceutical Services

Programme. For base-case analysis, treatment effect of PD-1/L1 inhibitors was assumed to persist up to three years after completion of two years of treatment.

Hospitalisation costs for respiratory neoplasm from the MOH casemix data[73] was used as a proxy for estimating the cost of managing treatment-related severe adverse events and assumed to be incurred in the first cycle. Moreover, patients were assumed to receive their first dose of treatment in inpatient setting as to monitor for serious adverse event and continued the rest of the treatment cycle at day care clinics. End-of-life cost was not included as it was assumed those who were in terminal stage would be discharged home.

The cost for the routine follow-up visits also included laboratory investigation and imaging fees where appropriate. As PD-L1 testing is yet to be offered at MOH facilities, the testing cost was also incorporated in the model. All cost inputs were inflated to 2021 according to the Malaysian consumer price index.[74]

The health utility values associated with PF and PD states for those with NSCLC were taken from published literature.[53,75] The associated QALYs then was calculated by multiplying the survival time in each state and its corresponding health utility values. Table 19 lists all the key parameters inputted in the Markov model.

6.2.5 Sensitivity Analysis

One-way sensitivity analysis was performed to determine key drivers that have the biggest influence on the ICER generated in the base-case analysis. Each relevant parameter was varied one-by-one according to its estimated range based on the reported 95% CI or estimated minimum-maximum range from referenced source if available, or by varying it over a range of ±30 per cent of the base-case value. The results of the sensitivity analyses for both first-line and second-line treatment were presented in tornado diagrams.

Table 19: Model parameters

Parameter	Item	Base-case value	Sensitivity Range	Source
Direct medical costs				
Test (MYR):	PD-L1 testing	850	595 - 1,105	Private laboratory
Drug cost per 3-week cycle (MYR): *(BSA: 1.73 m2; body weight: 65kg; AUC 6; CrCl 70ml/min)*	Platinum doublet chemotherapy (squamous)	1,981.83	843.60 – 3,616.30	Consumer Price Guide[72]
	Platinum doublet chemotherapy (non-squamous)	1,474.81	843.60 – 2,106.03	
	Chemotherapy (second-line)	900.64	75.24 – 1,726.03	
Drug administration cost (MYR):	IV reconstitution & administration	75.56	-	Lee, 2016[76]
Disease management cost per 3-week cycle (MYR):	Follow-up visit	646.72	452.70 – 840.74	MOH, 2022[77]
	Routine laboratory test	220	-	Fees Act[78]
	Thyroid test	65	-	
	CT scan - thorax	570	-	
	Best supportive care	466.5	326.55 – 606.45	Dranitsaris, 2011[79]
***Inpatient hospitalisation cost (MYR):**	Respiratory neoplasm - SOI 1	5,081.42	-	MOH Casemix Data[73]
	Respiratory neoplasm - SOI 2	6,832.67	-	
	Respiratory neoplasm - SOI 3	14,295.43	-	
Clinical effectiveness				
First-line treatment effects for squamous NSCLC:				
Low to intermediate PD-L1 expression (TPS 1 - 49%)				Fukuda, 2021[42]
OS	Pembrolizumab plus chemotherapy	0.57	0.36, 0.90	
PFS	Pembrolizumab plus chemotherapy	0.56	0.32, 0.97	

Parameter	Item	Base-case value	Sensitivity Range	Source
High expression PD-L1 expression (TPS ≥ 50%)				
OS	Pembrolizumab monotherapy	0.73	0.38, 1.4	He, 2022[41]
	Pembrolizumab plus chemotherapy	0.79	0.51, 1.2	
	Atezolizumab plus chemotherapy	0.48	0.29, 0.80	
PFS	Pembrolizumab monotherapy	0.45	0.26, 0.78	
	Pembrolizumab plus chemotherapy	0.37	0.24, 0.58	
	Atezolizumab plus chemotherapy	0.41	0.25, 0.68	
First-line treatment effects for non-squamous NSCLC:				
Low to intermediate PD-L1 expression (TPS 1 - 49%)				
OS	Pembrolizumab plus chemotherapy	0.55	0.34, 0.89	Fukuda, 2021[42]
	Atezolizumab plus chemotherapy	0.7	0.45, 1.08	
PFS	Pembrolizumab plus chemotherapy	0.55	0.37, 0.81	
	Atezolizumab plus chemotherapy	0.68	0.59, 0.80	
High expression PD-L1 expression (TPS ≥ 50%)				
OS	Pembrolizumab monotherapy	0.58	0.41, 0.83	He, 2022[41]
	Pembrolizumab plus chemotherapy	0.42	0.26, 0.68	
	Atezolizumab plus chemotherapy	0.81	0.52, 1.3	
PFS	Pembrolizumab monotherapy	0.55	0.39, 0.77	
	Pembrolizumab plus chemotherapy	0.36	0.25, 0.52	
	Atezolizumab plus chemotherapy	0.5	0.35, 0.72	

Parameter	Item	Base-case value	Sensitivity Range	Source
Second-line treatment effects (TPS ≥ 1%):				
OS	Pembrolizumab	0.66	0.57, 0.77	Passiglia, 2018[45]
	Atezolizumab	0.69	0.57, 0.85	
	Nivolumab	0.62	0.48, 081	
PFS	Pembrolizumab	0.83	0.74, 0.94	
	Atezolizumab	0.89	0.75, 1.06	
	Nivolumab	0.69	0.55, 0.87	
Probabilities of serious treatment-related AEs:				
First-line (squamous)	Platinum doublet chemotherapy	0.132	0.092 – 0.172	Paz-Ares, 2020[65]
	Pembrolizumab monotherapy	0.227	0.159 – 0.295	Reck, 2021[80]
	Pembrolizumab + chemotherapy	0.273	19.11 – 0.355	Paz-Ares, 2020[65]
	Atezolizumab + chemotherapy	0.232	0.162 – 0.302	Jotte, 2020[81]
First-line (non-squamous)	Platinum doublet chemotherapy	0.163	0.114 – 0.212	Gadgeel,2020[66]
	Pembrolizumab monotherapy	0.227	0.159 – 0.295	Reck, 2021[80]
	Pembrolizumab + chemotherapy	0.336	0.235 – 0.437	Gadgeel,2020[66]
	Atezolizumab + chemotherapy	0.24	0.17 – 0.31	West, 2019[82]
Second-line	Chemotherapy	0.24	0.168 – 0.312	Brahmer, 2015[83]
	Pembrolizumab	0.113	0.079 – 0.147	Herbst, 2021[67]
	Atezolizumab	0.33	0.231 – 0.429	Mazieres, 2020[84]
	Nivolumab	0.07	0.049 – 0.091	Brahmer, 2015; Borghaei, 2015[83,18]
Health state utility values				
First-line treatment:	PF state	0.804	0.643 - 0.965	Nafees, 2016[75]
	PD state	0.321	0.257 - 0.385	
Second-line treatment: 1. Docetaxel	PF state	0.55	0.431 - 0.940	Leung, 2022[53]
	PD state	0.37	0.184 - 0.900	

Parameter	Item	Base-case value	Sensitivity Range	Source
2. Pembrolizumab	PF state	0.756	0.425 - 0.843	Leung, 2022[53]
	PD state	0.52	0.430 - 0.520	
3. Atezolizumab	PF state	0.73	0.610 - 0.750	
	PD state	0.509	0.430 - 0.520	
4. Nivolumab	PF state	0.653	0.437 - 0.974	
	PD state	0.47	0.184 - 0.900	

BSA: body surface area; AUC: area under the curve; MOH: Ministry of Health; CT: computed tomography; SOI: severity of illness; OS: overall survival; PFS: progression-free survival; TPS: tumour proportion score; AEs: adverse events; PF: progression-free; PD: progressive disease
**SOI 1: no complication or comorbidity; SOI 2: with complication and comorbidity; SOI 3: with major complication and comorbidity*

6.3 RESULTS

6.3.1 Base-Case Analysis

In the first-line treatment setting, treatment with PD-1/L1 inhibitors in high PD-L1 expressors with squamous histology resulted in additional QALYs of 1.62, 0.88 and 0.43 for atezolizumab plus chemotherapy, pembrolizumab plus chemotherapy and pembrolizumab monotherapy, respectively. The incremental cost per patient compared to chemotherapy was the lowest with atezolizumab plus chemotherapy combination therapy at MYR 229,600, compared to that of pembrolizumab either as monotherapy or in combination with chemotherapy at MYR 398,200 and MYR 459,800, respectively. Hence, atezolizumab plus chemotherapy has generated the lowest ICER in this subpopulation at MYR 141,500 (~three times the set threshold). In squamous NSCLC population with low to intermediate PD-L1 expression level, the additional cost per patient to gain one QALY in comparison to chemotherapy was projected to be around MYR 373,200.

On the other hand, high PD-L1 expressors with non-squamous NSCLC treated with pembrolizumab in combination with chemotherapy, were projected to benefit from the largest improvement in QALY with additional of 1.87 QALYs when compared to conventional chemotherapy. Despite the combination therapy resulting in the highest cost of treatment per patient, the estimated ICER was the lowest, which was about MYR 263,700 (~5.6 times the set threshold), compared to that of pembrolizumab monotherapy and atezolizumab plus chemotherapy regimen. Similarly, pembrolizumab plus chemotherapy regimen was observed to yield the lowest ICER in comparison to conventional chemotherapy in advanced metastatic non-squamous NSCLC patients with low to intermediate level of PD-L1 expression. As presented in Table 20, while the incremental cost associated with atezolizumab plus chemotherapy regimen compared to chemotherapy was much lower than that of pembrolizumab plus chemotherapy regimen, the additional QALY gained (in comparison to reference strategy) with the latter was more substantial, 1.07 QALY versus that estimated of the former, 0.19 QALY.

Table 20: Summary of costs and outcomes results in base-case analysis for first-line interventions

Strategy	Total cost (MYR)	Progression-free LYs	Overall LYs	QALYs	*ICER (MYR/QALY)
Squamous NSCLC:					
Platinum-based chemotherapy (reference strategy)	31,807.04	0.64	1.76	0.84	-
High PD-L1 expression level:					
1. Atezolizumab plus chemotherapy	264,135.61	2.15	4.45	2.46	141,466.11
2. Pembrolizumab monotherapy	429,978.39	1.60	1.76	1.27	921,381.12
3. Pembrolizumab plus chemotherapy	491,629.47	1.94	2.12	1.53	671,958.10
Low to intermediate PD-L1 expression level:					
Pembrolizumab plus chemotherapy	407,577.99	1.43	3.72	1.72	425,215.06
Non-squamous NSCLC:					
Platinum-based chemotherapy (reference strategy)	31,082.96	0.65	1.94	0.89	-
High PD-L1 expression level:					
1. Atezolizumab plus chemotherapy	211,312.07	1.55	1.94	1.29	446,335.65
2. Pembrolizumab monotherapy	399,479.12	1.57	4.21	1.89	369,551.86
3. Pembrolizumab plus chemotherapy	524,448.19	2.74	5.84	2.76	263,731.04
Low to intermediate PD-L1 expression level:					
1. Atezolizumab plus chemotherapy	175,484.40	1.06	1.94	1.08	766,741.99
2. Pembrolizumab plus chemotherapy	410,142.95	1.58	4.47	1.96	355,885.70

**In comparison to reference strategy*

LY: life years; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio

Table 21 illustrated a summary of cost-effectiveness results in the second-line setting. The treatment with atezolizumab was predicted to result in the lowest cost of treatment. However, it was also associated with the lowest improvement in QALYs gained when compared to the conventional second-line chemotherapy with incremental QALYs of 0.58 versus that of pembrolizumab and nivolumab (0.71 and 0.69, respectively). Conversely, pembrolizumab projected marginally better improvement in QALYs compared to the other two interventions, with an ICER that was about similar to that of nivolumab. Overall, none of the interventions was cost-effective at the assumed threshold.

Table 21: Summary of cost and outcome results in base-case analysis for second-line interventions

Strategy	Total cost (MYR)	Progression-free LYs	Overall LYs	QALYs	*ICER (MYR/QALY)
Chemotherapy (reference strategy)	26,968.94	0.60	1.14	0.52	-
Atezolizumab	126,281.88	0.64	2.01	1.10	170,483.29
Nivolumab	187,406.41	1.07	2.33	1.21	231,878.81
Pembrolizumab	189,325.28	0.82	2.14	1.23	227,604.62

**In comparison to reference strategy*
LY: life years; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio

6.3.2 Scenario Analysis

Two scenario analyses were conducted to test the assumptions of the model in the base-case analysis. In the first scenario, it was assumed that MOH were to provide the treatment for a duration in which it was estimated that 50 per cent of patients would have progressed. Hence, the beneficial treatment effect was expected to be smaller as well. In the second scenario, the duration of treatment was similar to the first scenario, with additional assumptions that patient would need to pay out-of-pocket for one course of treatment only and the testing cost for PD-L1 expression was inclusive of the drug costs. The cost-effectiveness results of the two scenarios were as displayed in Table 22 and Table 23. Despite considerable reduction in the total cost of treatment per patient, still none of the interventions was cost-effective at the given threshold.

Table 22: Cost-effectiveness results for scenario analyses (first-line setting)

PD-L1 expression level	High PD-L1 expression level			Low to intermediate PD-L1 expression level		
Scenario	***Inc. cost (MYR)**	***Inc. QALYs**	**ICER (MYR/QALY)**	***Inc. cost (MYR)**	***Inc. QALYs**	**ICER (MYR/QALY)**
Scenario 1 Squamous:						
Atezolizumab plus chemotherapy	137,982.18	0.81	170,336.80			
Pembrolizumab monotherapy	232,291.45	0.34	692,733.22		NA	
Pembrolizumab plus chemotherapy	296,866.30	0.44	671,745.17	201,887.83	0.56	363,165.90
Non-squamous:						
Atezolizumab plus chemotherapy	95,701.56	0.31	307,826.54	73,763.69	0.16	468,928.83
Pembrolizumab monotherapy	193,104.33	0.72	268,790.79		NA	
Pembrolizumab plus chemotherapy	298,303.86	1.20	248,326.75	202,685.24	0.76	267,154.84
Scenario 2 Squamous:						
Atezolizumab plus chemotherapy	125,413.15	0.81	154,820.54			
Pembrolizumab monotherapy	206,754.42	0.34	616,577.41		NA	
Pembrolizumab plus chemotherapy	271,036.60	0.44	613,298.06	176,747.01	0.56	317,941.34

PD-L1 expression level	High PD-L1 expression level			Low to intermediate PD-L1 expression level		
Scenario	***Inc. cost (MYR)**	***Inc. QALYs**	**ICER (MYR/QALY)**	***Inc. cost (MYR)**	***Inc. QALYs**	**ICER (MYR/QALY)**
Scenario 2						
Non-squamous:						
Atezolizumab plus chemotherapy	83,524.83	0.31	268,659.76	61,965.22	0.16	393,923.88
Pembrolizumab monotherapy	168,472.95	0.72	234,505.25		NA	
Pembrolizumab plus chemotherapy	272,806.39	1.20	227,101.06	178,053.86	0.76	234,688.78

Inc: incremental; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; TPS: tumour proportion score; NA: not applicable
** Incremental cost and QALYs compared to reference strategy*

Table 23: Cost-effectiveness results for scenario analyses (second-line setting)

Scenario	*Inc. cost (MYR)	*Inc. QALYs	ICER (MYR/QALY)
Scenario 1			
Atezolizumab	47,798.70	0.45	105,937.18
Nivolumab	81,278.49	0.50	163,389.54
Pembrolizumab	75,821.51	0.55	138,854.85
Scenario 2			
Atezolizumab	36,839.58	0.45	81,648.26
Nivolumab	71,557.66	0.50	143,848.31
Pembrolizumab	60,545.24	0.55	110,878.83

*Inc: incremental; QALY: quality-adjusted life years; ICER: incremental cost-effectiveness ratio; TPS: tumour proportion score * Incremental cost and QALYs compared to reference strategy*

6.3.3 SENSITIVITY ANALYSIS

The tornado diagrams illustrated parameters that have remarkable impact on the ICER estimation in the base-case scenario. In squamous NSCLC patients, as presented in Figure 14, three main parameters identified were cost of the drugs and health utility values associated with PF and PD states, regardless of the level of PD-L1 expressions. Similar results were also observed in the non-squamous NSCLC population, regardless of PD-L1 expression (Figure 15). As expected, lower drug cost would likely drive the ICER closer to the threshold value. On the other hand, higher value associated with the PF and PD states would increase the likelihood of these interventions to be cost-effective.

In the second-line setting, the key parameters identified were as presented in tornado diagrams in Figure 16. Higher utility value associated with PF and PD states in the comparator arm for all interventions appeared to drive the ICER further from the set threshold. Likewise, cost of the drug also played a major role in the variability of the ICER generated, where lower cost would have resulted in lower ICER.

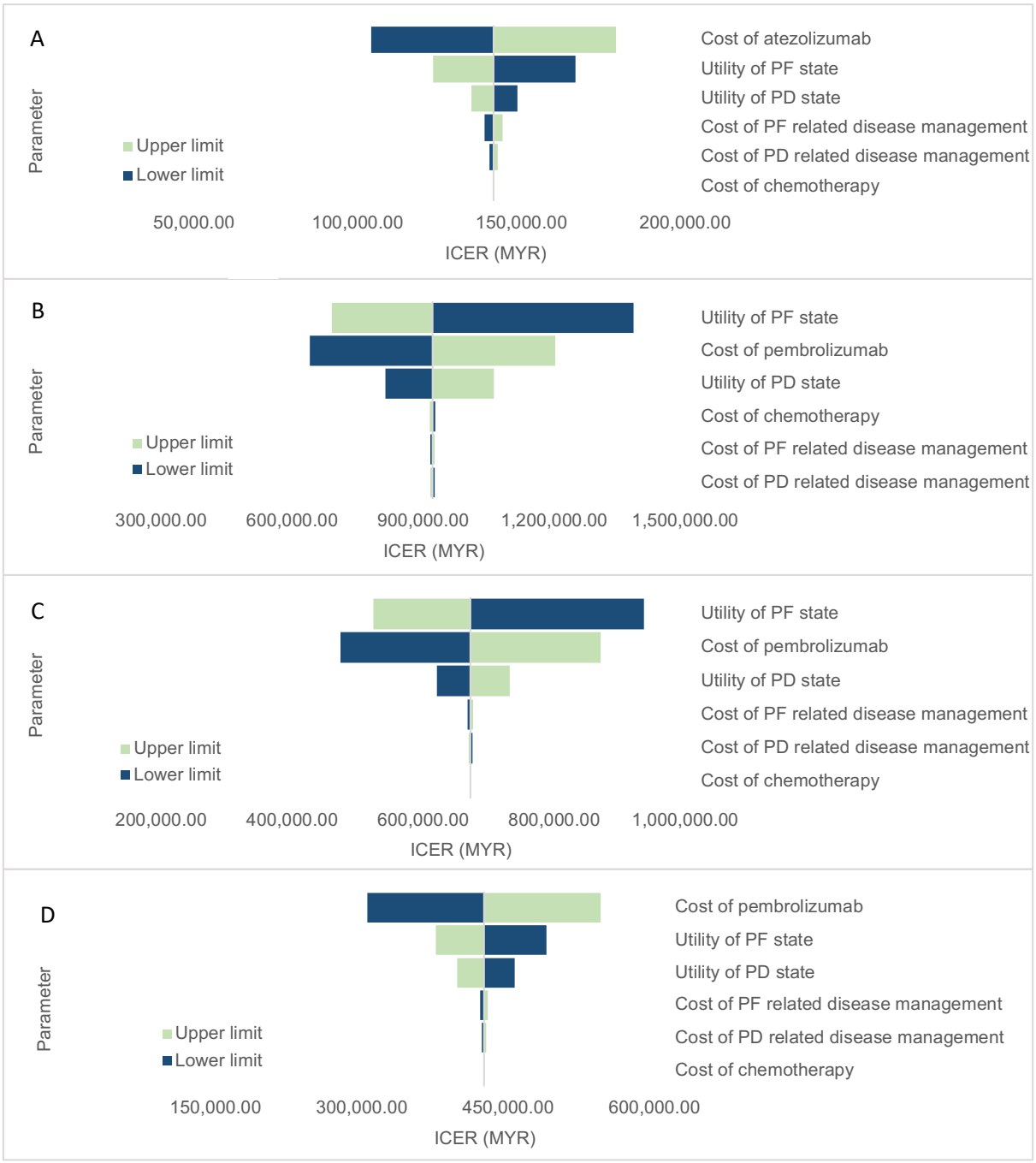


Figure 14: Tornado diagrams for PD-1/L1 inhibitors use in first-line setting for squamous NSCLC.

High PD-L1 expression: **(A)** Atezolizumab plus Chemotherapy vs Chemotherapy **(B)** Pembrolizumab monotherapy vs Chemotherapy **(C)** Pembrolizumab plus Chemotherapy vs Chemotherapy;

Low-intermediate PD-L1 expression: **(D)** Pembrolizumab plus Chemotherapy vs Chemotherapy

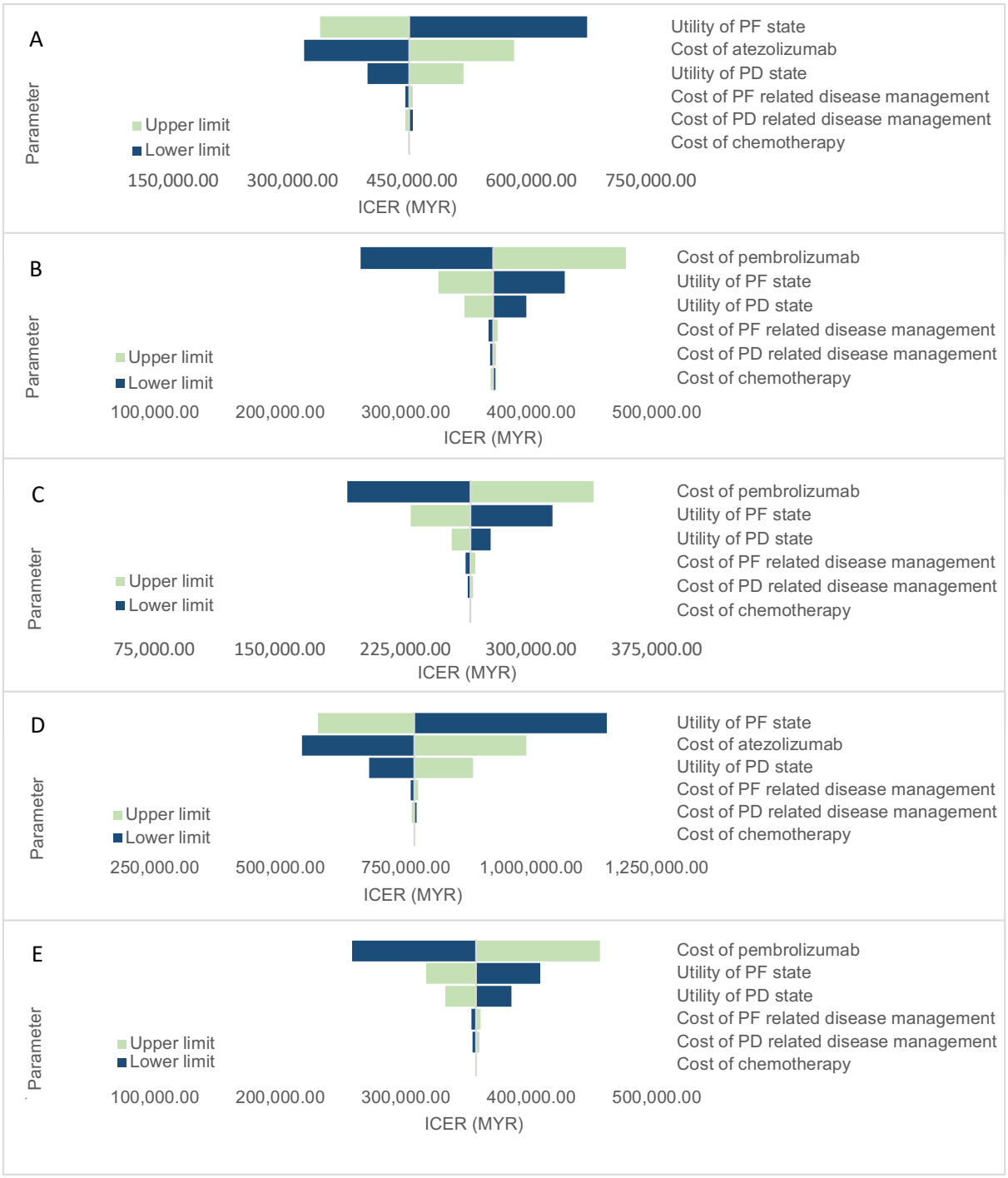


Figure 15: Tornado diagrams for PD-1/L1 inhibitors use in first-line setting for non-squamous NSCLC.

High PD-L1 expression: **(A)** Atezolizumab plus Chemotherapy vs Chemotherapy **(B)** Pembrolizumab monotherapy vs Chemotherapy **(C)** Pembrolizumab plus Chemotherapy vs Chemotherapy;

Low-intermediate PD-L1 expression: **(D)** Atezolizumab plus Chemotherapy vs Chemotherapy **(E)** Pembrolizumab plus Chemotherapy vs Chemotherapy

**PD: progressive disease; PF: progression-free*

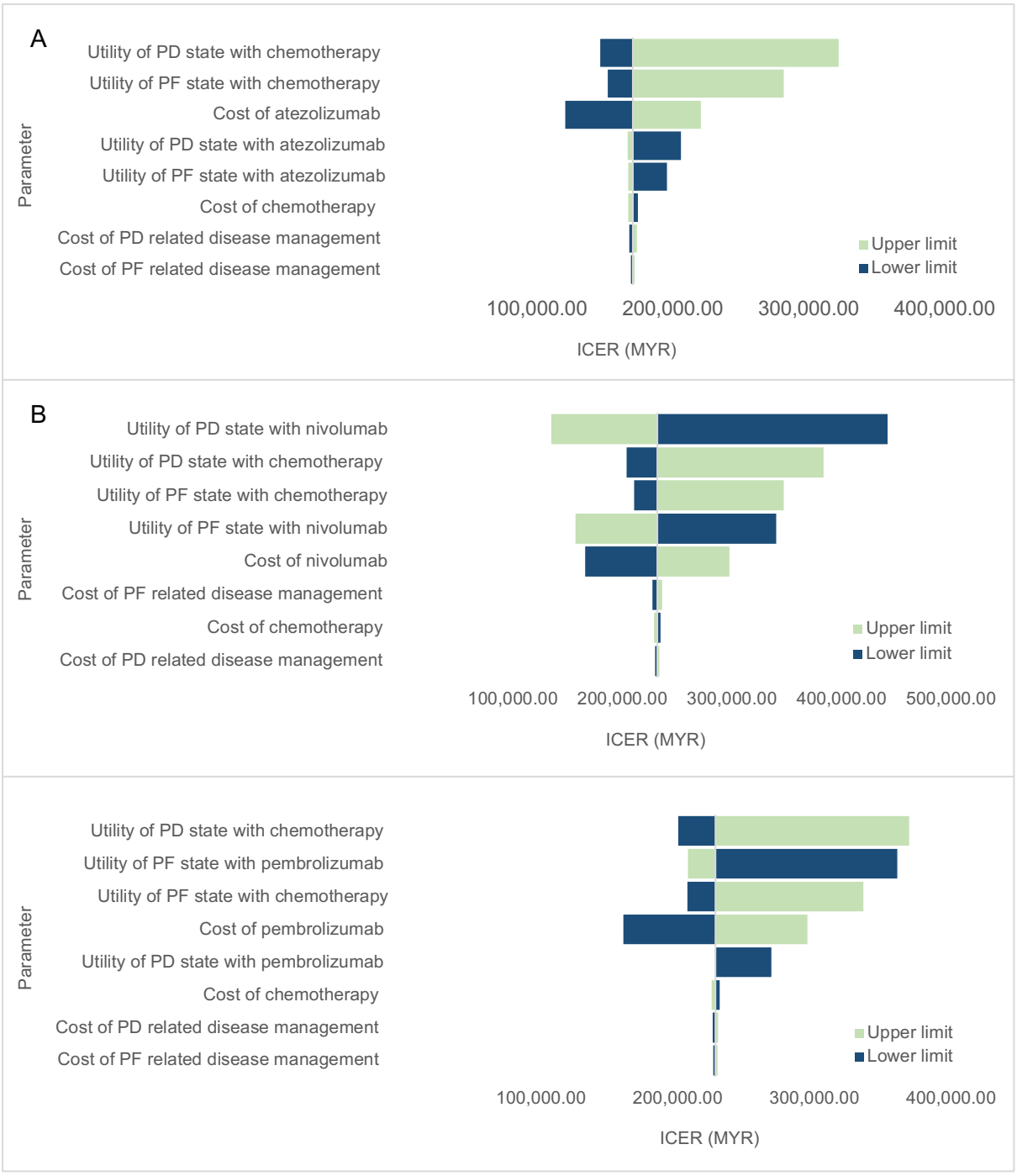


Figure 16: Tornado diagrams for PD-1/L1 inhibitors use in second-line setting. **(A)** Atezolizumab vs Chemotherapy; **(B)** Nivolumab vs Chemotherapy; **(C)** Pembrolizumab vs Chemotherapy

**PD: progressive disease; PF: progression-free*

6.4 DISCUSSION

Overall, in the base-case analysis, in comparison to conventional chemotherapy either as first-line or second-line treatment, none of the interventions was found to be cost-effective from the MOH perspective at the current threshold. The cost-effectiveness results were consistent with findings from previous CEA studies cited in Part A of this report where it was noted that much higher WTP is needed for PD-1/L1 inhibitors therapy to be cost-effective from public payers' perspective.

Similarly, the results from scenario analyses also showed that all interventions either in the first-line or second-line setting were not cost-effective at the given threshold. While scenario 2 tried to explore the impact of ICER if patient co-payment exists, in practice this would be difficult to be applied in MOH setting as the financial burden associated with PD-1/L1 inhibitors are too high, given the mean monthly salaries and wages received by employees in Malaysia was only MYR 3,037[85]. Furthermore, one previously published CE study also assessed the economic impact of incorporating patient assistance programme and found that the estimated ICER was still higher than the threshold set for the country.[71] Results from the conducted one-way sensitivity analysis also showed that cost of the drugs was one of the parameters with substantial influence on the ICERs generated.

Although this CEA has attempted to incorporate as much input relevant to Malaysian population as accessible, the use of PD-1/L1 inhibitors for treatment of NSCLC in Malaysia, especially in MOH setting is very limited. Hence, the results presented in this CEA should be interpreted with cautious as trial-based clinical effectiveness data and extrapolation of treatment effect over chosen time horizon using selected parametric survival distribution may have underestimated or overestimated the estimated costs and outcomes, hence affecting the resulting ICERs for the interventions described above.

7.0 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 $\geqslant$ USD100,000. Based on the economic evaluation conducted from the perspective of MOH, at the given ICER threshold, PD-1/PD-L1 inhibitors therapy is not cost-effective compared to the current conventional chemotherapy either as a first- or second-line treatment for Malaysians suffering from advanced metastatic NSCLC, regardless of PD-L1 expression level.

8.0 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.

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APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES/ DIAGNOSTIC 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

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HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL
Immunotherapy For PD-L1 Positive Non-Small Cell Lung Cancer

1.0 BACKGROUND INFORMATION

1.1 Introduction

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.[1] In Malaysia, lung cancer is the third most common cancer, accounting for 9.8% of cancer cases.[2] Most lung cancer cases in Malaysia are diagnosed at an advanced stage (stage III or stage IV).[2, 3] According to Malaysia National Cancer Registry Report, between 2012 to 2016, 78.1% of male and 81.3% of female lung cancer patients were diagnosed with Stage IV lung cancer.[2] 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). [4] The NSCLC which accounts for nearly 85% of all cases of lung carcinoma consists of various histological subtypes (WHO classification of tumours of the lung reference). These histological subtypes include adenocarcinoma and squamous cell carcinoma (SCC). Adenocarcinoma is the most common histological subtype of lung carcinomas diagnosed within the Malaysian population. [3, 5]

Until recently, the standard first-line treatments for NSCLC with no driver mutations [epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK) or receptor tyrosine kinase (ROS1) genomic aberrations] was doublet platinum-based 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).[6-9] 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 immune-oncologic drugs either as single agent or in combination with chemotherapy for the first line treatment of NSCLC, based on treatment history, genetic alterations, histology and level of programmed cell death ligand-1 (PD-L1) expression.[10, 11]

1.2 Description of Technology : Immune Checkpoint Inhibitors

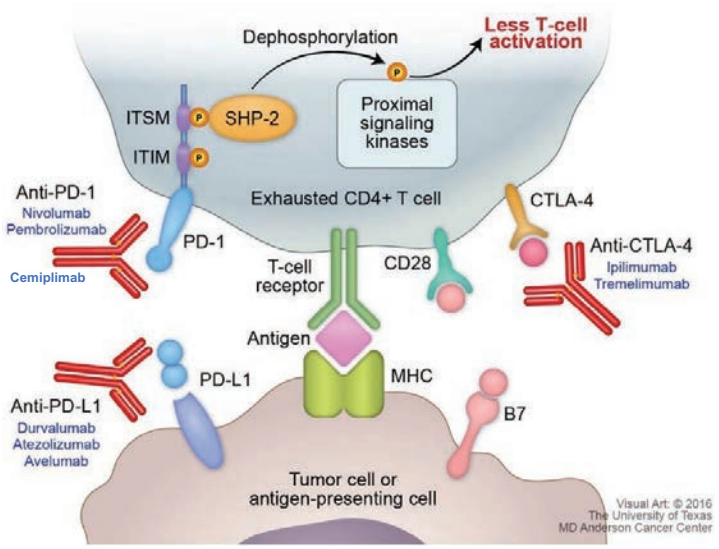
One of the theory of tumour invasion and metastasis is immune evasion The immune system has the ability to suppress tumour growth by eliminating cancer cells. However, it can also promote tumour growth by selecting cancer cells that able evade immune surveillance. Tumour cells can escape the immune system attack by forming immune checkpoints.[12] The most studied immune checkpoint receptors are the inhibitory receptors anti-cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1).[10] Blocking the immune checkpoints can activate the immune system and prevent tumour cell evasion. This discovery has introduced a new era in cancer treatment.[12]

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, to prevent an excessive and uncontrolled immune response.[9] Their inhibition activates T-lymphocytes and enhances the adaptive anti-cancer immune response. To date, six ICIs 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.[11] (Figure 1) Nivolumab, pembrolizumab, atezolizumab, durvalumab and cemiplimab have shown significant anti-tumour activity in NSCLC.[9] Their FDA approved indications for advanced/metastatic NSCLC are listed in Table 1.

PD-L1 Testing

PD-L1 expression on immune cells or tumour cells is used as predictive biomarkers for response to ICI treatment. PD-L1 expression ranges from 23–27% in non-squamous NSCLC and from 19–56% in squamous NSCLC.[13] A local multicentre study involving public, private and university hospitals reported 61% of their participants with NSCLC without driver mutation tested positive for PD-L1 expressor gene.[3] As of December 2020, there are five companion or complementary diagnostic device for PD-L1 expression level that have been approved to identify patients across seven tissue types.[11] The range of companion/complementary PD-L1 Immunohistochemistry (IHC) which have been approved for its paired drug is shown in Table 2. Formalin-fixed and paraffin-embedded (FFPE) sections of biopsies or resected specimens and cell blocks of fine-needle aspirations (FNAs) or effusion specimens can be used for IHC testing of PD-L1. Liquid biopsies (utilising circulating tumour cells) are not recommended currently.[14] The expanded use of diagnostic assay across different immuno-oncologic products and tumour types is also not recommended.[11] These different

assays have been developed independently using different diagnostic antibodies, protocols, reagents, cell types, and detection systems, therefore, associated with specific drugs. The scoring metrics and PD-L1 thresholds that determine a biomarker-positive patient differs across different assays. [14]



*ITSM=immunoreceptor tyrosine-based switch motif; ITIM=immunoreceptor tyrosine-based inhibitory motif; CD28=cluster of differentiation 28; MHC=major histocompatibility complex; SHP-2=Src homology 2 (SH2) domain containing non-transmembrane PTP.

Figure 1: PD-1/PD-L1 pathway and immunotherapy targets[15]

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Table 1: Immune Checkpoint Inhibitors (ICIs) Targeting PD-1/PD-L1 Pathway Approved by FDA for Use in NSCLC[11, 16]

ICI	FDA-approved indication	Date of approval
Pembrolizumab (*Keytruda)* - humanised, IgG4 monoclonal antibody against PD- 1 receptor	Metastatic NSCLC patients who progressed after platinum-based therapy or EGFR- or ALK-targeted therapy and are positive for PD-L1	2 October 2015
	First-line treatment for metastatic NSCLC with high PD-L1 expression (≥ 50%) without no EGFR or ALK mutation	24 October 2016
	First-line treatment in combination with pemetrexed and carboplatin for metastatic non-squamous NSCLC without EGFR or ALK mutation, regardless of PD-L1 expression	10 May 2017
	First-line treatment in combination with carboplatin with paclitaxel/nab-paclitaxel for metastatic squamous NSCLC, regardless of PD-L1 expression	30 Oct 2018
	First-line monotherapy for patients with stage 3 NSCLC who cannot undergo surgical resection/ chemoradiation or metastatic NSCLC with PD-L1 expression ≥1% and no EGFR or ALK mutation	11 April 2019
Nivolumab (*Opdivo)* - human immunoglobulin (Ig) G4 antibody against PD-1 receptor	**Squamous** NSCLC with progression after platinum-doublet chemotherapy, regardless of PD-L1 expression	4 Mac 2015
	Metastatic non-squamous NSCLC with progression on first-line platinum-based chemotherapy	10 October 2015
Atezolizumab (*Tecentriq)* - human monoclonal IgG1 antibody directed against PD-L1	**Metastatic NSCLC** with progression on platinum-based chemotherapy, and in progression on targeted therapy in patients with EGFR or ALK abnormalities.	18 October 2016
	Metastatic non-squamous NSCLC without EGFR or ALK mutation in combination with carboplatin, paclitaxel, and bevacizumab	6 December 2018
Durvalumab (*Imfinzi)* - selective, high- affinity human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80	**Surgically unresectable stage III** NSCLC with no progression after treatment with chemoradiation	16 February 2018
Cemiplimab (*Libtayo*)[16] - human immunoglobulin (Ig) G4 antibody against PD-1 receptor	**First-line treatment** for patients with NSCLC whose tumours have high PD-L1 expression [Tumor Proportion Score (TPS) ≥ 50%] as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations, and is: - locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or - metastatic	22 February 2021

Table 2: PD-L1 IHC assays according to drugs and diagnostic tests

Companion Diagnostic Assay	Paired ICI	PD-L1 diagnostic antibody clone	PD-L1 binding domain	Platform	Second line criteria for PD-L1 positivity
Agilent PD- L1 IHC 22C3 pharmDx[17, 18]	1. Pembrolizumab 2. Cemiplimab	22C3 (mouse)	Extracellular	Link 48 Autostainer	≥ 50% tumour cells
PD-L1 IHC 28-8 pharmDx[17]	Nivolumab	28-8 (rabbit)	Extracellular	Link 48 Autostainer	≥ 1% tumour cells
Ventana PD-L1 (SP142) [17]	Atezolizumab	SP142 (rabbit)	Cytoplasmic	BenchMark ULTRA	Tumour cells and/or tumour infiltrating immune cells
Ventana PD-L1 (SP263)[17]	Durvalumab	SP263 (rabbit)	Extracellular	BenchMark	≥ 25% tumour cells
Dako PD-L1 IHC 73-10[19]	Avelumab	73-10 (rabbit)	Unknown	Dako assay	≥ 1% tumour cells

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

In Malaysian public hospitals, patients with advanced and metastatic NSCLC without driver mutations are commonly treated with platinum doublet chemotherapy. Cisplatin-based chemotherapy is used in patients with good Eastern Cooperative Oncology Group (ECOG) performance status.[20] Combination of pembrolizumab and chemotherapy is approved for first-line treatment advanced NSCLC regardless of PD-L1 expression, and pembrolizumab alone is approved for the first line in patients with PD-L1 expression of at least 1%.[3, 21] Durvalumab is registered for use in patients with stage III lung cancer after chemo-radiotherapy. Atezolizumab, nivolumab and pembrolizumab are approved as second-line treatments in patients who fail chemotherapy.[21] These ICIs and their companion/complementary testing are currently not subsidized by Malaysian government.[3] 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. Most private hospitals perform PD-L1 immunohistochemistry as reflex testing and pembrolizumab is the commonly prescribed ICI in the first line setting for NSCLC.[3] 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. The cost of the ICI treatment ranges from US$2400 to US$4200 (RM10,490 to RM18,358; *currency conversion as of 25 May 2022*) every 3 weeks alone, without the inclusion of medical consultation and hospitalisation costs.[3] Immune checkpoint inhibitors approved in Malaysia for advanced/metastatic NSCLC as well as their reimbursement status, are listed in Table 3. The current review will evaluate three ICIs approved for use in Malaysia. Durvalumab will be excluded from the review as the intended NSCLC population for its use differs from the population of interest in this review.

Table 3: Immune Checkpoint Inhibitors Approved in Malaysia for Advanced/Metastatic NSCLC and Their Reimbursement Status[21, 22]

Immune Checkpoint Inhibitor (brand name, distributor)	Approved as First Line Treatment	Approved as Second Line Treatment	Available for free (Public Hospital)	Reimbursement (Private Insurance)
Pembrolizumab (*Keytruda, MSD Malaysia*)	Yes	Yes	No	Yes
Nivolumab (*Opdivo, Bristol Myers Squibb – distributed by DKSH Malaysia)*	No	Yes	No	Yes
Atezolizumab (*Tecentriq, Roche*)	No	Yes	No	Yes
Durvalumab (*Imfinzi, AstraZeneca*)	Yes	No	No	Yes

2.0 POLICY QUESTIONS:

2.1 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?

2.2 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?

3.0 OBJECTIVES:

3.1 To assess the comparative effectiveness and safety of immune checkpoint inhibitors in treating PD-L1 positive patients with advanced and metastatic NSCLC.

3.2 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.

Research questions

i. How effective and safe are the immune checkpoint inhibitors in the treatment of PD-L1 positive patients with advanced and metastatic NSCLC?

ii. How cost-effective are the immune checkpoint inhibitors for the treatment of advanced and metastatic NSCLC?

iii. What are the organisational, ethical and social implications of implementing this treatment option in Ministry of Health hospitals?

4.0 METHODS:

4.1 Search Strategy

Electronic databases will be searched for published literature pertaining to immune checkpoint inhibitors for the treatment of NSCLC.

4.1.1 Databases are as follows: MEDLINE, EMBASE, PubMed, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, 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 literature will be identified from the references of the retrieved 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 limitations applied in the search such as year and language. The search strategy will be included in the appendix.

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4.2 Inclusion and exclusion criteria

4.2.1 Inclusion criteria

POPULATION	Patient with advanced and metastatic (stage IIIB / IV) NSCLC who are positive for PD-L1 expression **Subpopulation** based on histological type: 1. Squamous 2. Non-squamous
INTERVENTION	Immune Checkpoint Inhibitors (ICI) (Atezolizumab, Pembrolizumab, Nivolumab), either as - single agent, or - combination with chemotherapy
COMPARATOR	Standard first line chemotherapy (platinum-based chemotherapy)
OUTCOMES	**i. Effectiveness** - overall survival (OS) - progression free survival (PFS) - objective response rate (ORR) - health-related quality of life (HRQoL) **ii. Safety** - treatment-related adverse events (TRAE) **iii. Economic impact** - Cost effectiveness analysis - Cost utility analysis - Cost benefit analysis - Cost analysis - Any other measure of economic outcomes iv. **Organisational, ethical and social implications**
STUDY DESIGN	HTA reports, systematic review with/out meta-analysis, randomised controlled trial (RCT) and economic evaluation studies.
English full text articles	

4.2.2 Exclusion criteria

a) Study design: Animal study, laboratory study, narrative review, cohort, case-control, cross-sectional, qualitative studies
b) Non-English full-text articles

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 risk of bias of all retrieved literatures will be assessed using the relevant checklist of the Cochrane Risk of Bias tool.

4.4 Analysis and Synthesis of Evidence

4.4.1 Data extraction strategy

The following data will be extracted:

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

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 outcome measures will be presented in a tabulated format with narrative summaries. Meta-analysis may be conducted for this Health Technology Assessment.

5.0 REPORT WRITING

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14. Rajadurai P, Cheah PL, How SH et al. Molecular testing for advanced non-small cell lung cancer in Malaysia: Consensus statement from the College of

Pathologists, Academy of Medicine Malaysia, the Malaysian Thoracic Society, and the Malaysian Oncological Society. Lung Cancer. 2019;136:65-73.
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APPENDIX 3: SEARCH STRATEGY

Database: Ovid MEDLINE(R) ALL <1946 to July 28, 2022>

Search strategy

#	Search Details	Results
1	CARCINOMA, NON-SMALL-CELL LUNG/	67089
2	(carcinoma adj1 non small cell lung).tw	14386
3	(carcinoma$1 adj1 non-small-cell lung).tw	5816
4	(lung carcinoma$1 adj1 non-small-cell).tw	5729
5	(non-small cell lung adj1 (carcinoma or cancer)).tw	74318
6	(non-small-cell lung adj1 carcinoma$1).tw	5816
7	ADENOCARCINOMA/	161815
8	CARCINOMA, SQUAMOUS CELL/	138562
9	(squamous adj1 carcinoma$1).tw	8686
10	(squamous cell adj1 carcinoma$1).tw	115687
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	402261
12	PROGRAMMED CELL DEATH 1 RECEPTOR/	10914
13	((pd1 or pd-1) adj protein).tw	126
14	((pd 1 or pd-1 or pd1) adj1 receptor).tw	895
15	(programmed cell death 1 adj (protein or receptor)).tw	165
16	programmed cell death protein 1.tw	3061
17	12 or 13 or 14 or 15 or 16	13431
18	IMMUNOTHERAPY/	60229
19	immunotherap*.tw	116968
20	IMMUNE CHECKPOINT INHIBITORS/	7249
21	(immune adj1 (blockade or blockers)).tw	63
22	(immune adj1 'checkpoint inhibit*').tw	18188
23	((pd 1 or pd-1) adj1 inhibitor$1).tw	1993
24	18 or 19 or 20 or 21 or 22 or 23	151137
25	11 and 17 and 24	1616
26	limit 25 to humans	**1435**
27	"COSTS AND COST ANALYSIS"/	50951
28	(cost adj1 analys#s).tw	8947
29	(cost analys#s adj2 cost$1).tw	8479
30	(cost minimi#ation adj1 analys#s).tw	854
31	(cost adj1 comparison$1).tw	1408
32	(cost adj1 measure$1).tw	811
33	COST BENEFIT ANALYSIS/	91041
34	(cost benefit adj1 data).tw	22
35	(cost adj1 effectiveness).tw	70176
36	(economic adj1 evaluation$1).tw	14264
37	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36	180748
38	25 and 37	**12**

Database: PUBMED

Search strategy

#	Search Details	Results
1	"carcinoma, non small cell lung"[MeSH Terms] OR ("carcinoma"[All Fields] AND "non small cell"[All Fields] AND "lung"[All Fields]) OR "non-small-cell lung carcinoma"[All Fields] OR ("non"[All Fields] AND "small"[All Fields] AND "cell"[All Fields] AND "lung"[All Fields] AND "carcinoma"[All Fields]) OR "non small cell lung carcinoma"[All Fields] OR "non small cell lung carcinoma"[Title/Abstract] OR "carcinoma, non small cell lung"[MeSH Terms] OR "non small cell lung carcinoma"[Text Word] OR ("adenocarcinoma"[MeSH Terms] OR "adenocarcinoma"[All Fields] OR "adenocarcinomas"[All Fields] OR "adenocarcinoma s"[All Fields]) OR "adenocarcinoma"[Title/Abstract] OR "adenocarcinoma"[MeSH Terms] OR "adenocarcinoma"[Text Word] OR ("carcinoma, squamous cell"[MeSH Terms] OR ("carcinoma"[All Fields] AND "squamous"[All Fields] AND "cell"[All Fields]) OR "squamous cell carcinoma"[All Fields] OR ("squamous"[All Fields] AND "cell"[All Fields] AND "carcinoma"[All Fields])) OR "squamous cell carcinoma"[Title/Abstract] OR "carcinoma, squamous cell"[MeSH Terms] OR "squamous cell carcinoma"[Text Word] OR ("non-squamous"[All Fields] AND ("cells"[MeSH Terms] OR "cells"[All Fields] OR "cell"[All Fields]) AND ("carcinoma"[MeSH Terms] OR "carcinoma"[All Fields] OR "carcinomas"[All Fields] OR "carcinoma s"[All Fields])) OR "non squamous cell carcinoma"[Title/Abstract] OR (("non-squamous"[All Fields] AND ("cells"[MeSH Terms] OR "cells"[All Fields] OR "cell"[All Fields])) AND "carcinoma"[MeSH Terms]) OR "non squamous cell carcinoma"[Text Word]	709,037
2	"programmed cell death 1 receptor"[MeSH Terms] OR "programmed cell death 1 receptor"[All Fields] OR "programmed cell death 1 protein"[All Fields] OR "programmed cell death 1 protein"[Title/Abstract] OR "programmed cell death 1 receptor"[MeSH Terms] OR "programmed cell death 1 protein"[Text Word] OR "programmed cell death 1 receptor"[MeSH Terms] OR "programmed cell death 1 receptor"[All Fields] OR "programmed cell death 1 receptor"[Title/Abstract] OR "programmed cell death 1 receptor"[MeSH Terms] OR "programmed cell death 1 receptor"[Text Word]	11,178
3	"immunotherapy"[MeSH Terms] OR "immunotherapy"[All Fields] OR "immunotherapies"[All Fields] OR "immunotherapy s"[All Fields] OR "immunotherapy"[Title/Abstract] OR "immunotherapy"[MeSH Terms] OR "immunotherapy"[Text Word] OR ("immune checkpoint inhibitors"[Pharmacological Action] OR "immune checkpoint inhibitors"[MeSH Terms] OR ("immune"[All Fields] AND "checkpoint"[All Fields] AND "inhibitors"[All Fields]) OR "immune checkpoint inhibitors"[All Fields] OR ("immune"[All Fields] AND "checkpoint"[All Fields] AND "inhibitor"[All Fields]) OR "immune checkpoint inhibitor"[All Fields]) OR "immune checkpoint inhibitor"[Title/Abstract] OR "immune checkpoint inhibitors"[MeSH Terms] OR "immune checkpoint inhibitor"[Text Word] OR ("immune checkpoint inhibitors"[Pharmacological Action] OR "immune checkpoint inhibitors"[MeSH Terms] OR ("immune"[All Fields] AND "checkpoint"[All Fields] AND "inhibitors"[All Fields]) OR "immune checkpoint inhibitors"[All Fields] OR ("PD1"[All Fields] AND "inhibitor"[All Fields]) OR "pd1 inhibitor"[All Fields]) OR "pd1 inhibitor"[Title/Abstract] OR "immune checkpoint inhibitors"[MeSH Terms] OR "pd1 inhibitor"[Text Word] OR ("immune checkpoint inhibitors"[Pharmacological Action] OR "immune checkpoint inhibitors"[MeSH Terms] OR ("immune"[All Fields] AND "checkpoint"[All Fields] AND "inhibitors"[All Fields]) OR "immune checkpoint inhibitors"[All Fields] OR ("pd"[All Fields] AND "l1"[All Fields] AND "inhibitor"[All Fields]) OR "pd l1 inhibitor"[All Fields]) OR "pd l1 inhibitor"[Title/Abstract] OR "immune checkpoint inhibitors"[MeSH Terms] OR "pd l1 inhibitor"[Text Word]	418,423
4	#1 AND #2 AND #3	**1097**

APPENDIX 4: LIST OF EXCLUDED STUDIES IN SYSTEMATIC REVIEW OF LITERATURE

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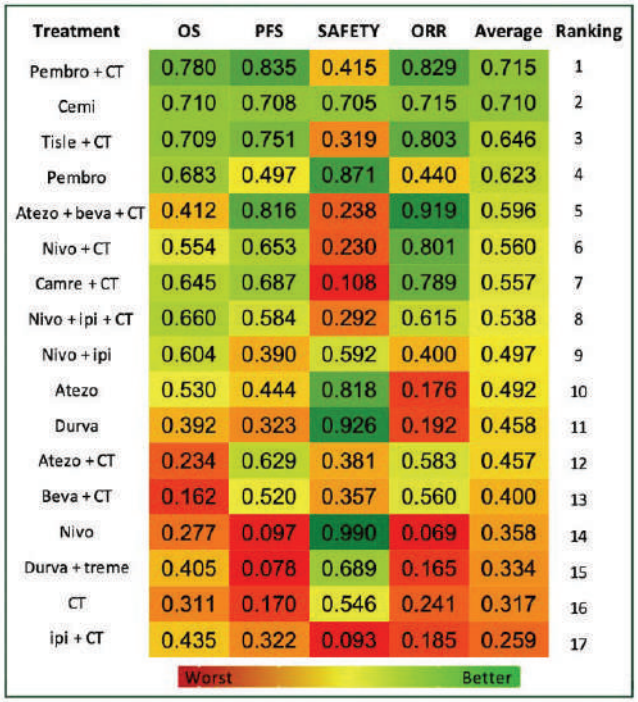
APPENDIX 5: EVIDENCE TABLE

Evidence Table : **EFFECTIVENESS AND SAFETY (IN TREATMENT NAÏVE POPULATION)**
Question : How effective and safe are Immune Checkpoint Inhibitors for the **first line treatment** of PD-L1 positive non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
1. Siciliano MA, Caridà G, Ciliberto D et al. **Efficacy and safety of first-line checkpoint inhibitors-based treatments for non-oncogene-addicted non-small-cell lung cancer: a systematic review and meta-analysis**. ESMO Open. 2022 Jun;7(3):14.	**Systematic review and network meta-analysis** **Objective** To investigate the efficacy and safety of ICI alone or in combination with CT and/or with another ICI as frontline treatment in NSCLC, **Study selection** **Inclusion criteria: (i)** phase II or III RCTs **(ii)** enrolled patients with either histologically or cytologically confirmed non-oncogene-addicted NSCLC **(iii)** compared 1 or more first-line treatments, including immunotherapy **(iv)** reported detailed outcomes including progression-free survival (PFS), OS, objective response rate (ORR) and treatment-related adverse events (TRAEs). **Exclusion criteria: (i)**Trials evaluating targeted therapy, radiotherapy, immune cells or cytokines. **(ii)** Analysis of selected population, maintenance strategy or health-related quality of life only. **Primary endpoints: (i)** OS (time from randomization to death from any cause) **(ii)** PFS (time from randomization to the date of objective disease progression or death from any cause in the absence of progression	I	19 RCTs involving 13,599 patients and 17 treatment regimens ***6 ICI monotherapy*** KEYNOTE-024 KEYNOTE-042 CheckMate-026, IMpower-110 MYSTIC Empower-Lung 1 ***12 ICI-CT*** KEYNOTE-189 KEYNOTE-407 KEYNOTE-021 cohort G NCT01285609 CameL, IMpower-130 IMpower-131 IMpower-132 IMpower-150 Checkmate-227 part II Rationale 304 Rationale 307 ***1 ICI-CT-AA*** IMpower-150 ***2 dual-ICI*** Checkmate-227 part I MYSTIC ***1 dual- ICI-CT*** CM-9LA **Phase II trial** 1 studies **Phase III trial** 18 studies **Sample size:** 60-637	**1. ICI monotherapy** - PEM - ATE - NIV - DUR - CEM **2. ICI-Chemo** - PEM-CT - ATE-CT - NIV-CT - IPI-CT - CAM-CT - TISLE-CT **3. Dual ICI** - NIV-IPI - DUR-TRE **4. Dual ICI-Chemo** - NIV-IPI-CT **5. ICI-AA-Chemo** - ATE-BEV-CT	Platinum based chemotherapy	Median 8.6-59.9 months	**OVERALL POPULATION** **Overall Survival (OS)** **Pooled HR (95% CI)** (*in comparison to CT*) ICI based treatment 0.78 (0.73-0.83) **SUCRA RANKING** PEM-CT 0.43 (0.23, 0.82) CEMI* 0.46 (0.15, 1.40) TISLE-CT* 0.46 (0.15, 1.40) PEM* 0.51 (0.23, 1.12) NIV-IPI-CT* 0.52 (0.17, 1.58) CAMRE-CT* 0.54 (0.18, 1.62) NIV-IPI* 0.58 (0.19, 1.75) NIV-CT* 0.66 (0.22, 1.99) ATE*. 0.69 (0.23, 2.09) IPI-CT* 0.83 (0.28, 2.52) ATE-BEVA-CT* 0.94 (0.17, 5.12) DURVA-TREME* 0.89 (0.29, 2.68) DURVA* 0.92 (0.31, 2.79) **Progression Free Survival (PFS)** **Pooled HR (95% CI)** (*in comparison to CT*) ICI based treatment 0.69 (0.62-0.77) **SUCRA RANKING** PEM-CT* 0.25 (0.06, 1.00) ATE-BEVA-CT 0.28 (0.17, 0.48) TISLE-CT 0.33 (0.17, 0.64) CEMI 0.35 (0.14, 0.87) CAMRE-CT 0.36 (0.14, 0.90) NIV-CT 0.39 (0.15, 0.96) ATE-CT 0.42 (0.25, 0.71) NIV-IPI-CT* 0.45 (0.18, 1.12) BEVA-CT* 0.50 (0.17, 1.44) PEM * 0.55 (0.28, 1.00) ATE * 0.59 (0.24, 1.48) NIV-IPI * 0.66 (0.26, 1.64) DURVA * 0.76 (0.31, 1.90) IPI-CT* 0.76 (0.28, 1.76)	**ICI** = Immunotherapy **CT** = Chemotherapy **AA**=Anti-angiogenesis **BEVA**= Bevacizumab **PEM**= Pembrolizumab **ATE**= Atezolizumab **NIV**= Nivolumab **DURVA**= Durvalumab **TRE**= Tremelimumab **CAM**= Camrelizumab **CEM**= Cemiplimab **TISLE** = tislelizumab **IPI**= Ipilimumab **BEV**= Bevacizumab * Not statistically significant

Bibliograph Citation	Study Type/ Methods	LE	er of Patients & t Characteristic	Intervention	Comparisc	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Commen
	and TRAEs [all grades al grade 3 (G3) or higher]. - A pairwise and a netwo meta-analysis (NMA) with a all-comers and a stratifie strategy were conducted. **Data source** PubMed, Embase, Cochrar Central Register of Controlle Trials and relevant abstrac and presentations of maj meeting databases (America Society of Clinical Oncolog the World Conference on Lur Cancer and the Europea Society for Medical Oncology A manual search was als carried out. Timeframe was s from January 2010 September 2021.		 **Figure 2. Ranking of treatments based on NMA.** All of the SUCRA values for each regimen with regard to PFS, OS, ORR and G3 or higher AEs. An average SUCRA and the average ranking are provided. **All of the SUCRA values for each regimen with regard to PFS, OS, ORR and G3 or higher AEs. An average SUCRA and the average ranking are provided. AE**, adverse event; **atezo**, atezolizumab; **beva**, bevacizumab; **camre**, camrelizumab; **cemi**, cemiplimab; **CT**, chemotherapy; **durva**, durvalumab; **ipi**, ipilimumab; **nivo**, nivolumab; **NMA**, network meta-analysis; **ORR**, overall response rate; **OS**, overall survival; **pembro**, pembrolizumab; **PFS**, progression-free survival; **SUCRA**, surface under the cumulative ranking curve; **tisle**, tislelizumab; **treme**, tremelimumab.			**Objective Response Rate (ORR)** **Pooled OR (95% CI)** *(in comparison to CT)* ICI based treatment 1.69 (1.39, 2.05) **SUCRA RANKING** ATE-BEVA-CT 0.09 (0.02, 0.40) PEM-CT 0.15 (0.08, 0.31) TISLE-CT 0.17 (0.10, 0.30) NIVO-CT 0.16 (0.06, 0.43) CAMRE-CT 0.17 (0.06, 0.45) CEMI 0.20 (0.08, 0.54) NIV-IPI-CT 0.29 (0.11, 0.77) ATE-CT 0.32 (0.18, 0.55) BEVA-CT* 0.34 (0.11, 1.05) PEM* 0.50 (0.25, 1.01) NIV-IPI* 0.60 (0.23, 1.58) The ICI-CT schedules ranked better than CT-free combinations. **Adverse Events (AEs)** **Pooled RR (95% CI)** *(in comparison to CT)* ICI based treatment 0.94 (0.90, 0.99) **SUCRA RANKING AEs≥G3** NIV 0.12 (0.07, 0.21) DURVA 0.19 (0.11, 0.34) PEM 0.26 (0.17, 0.38) ATE 0.33 (0.19, 0.57) CEMI 0.46 (0.27, 0.80) DURVA-TREME* 0.60 (0.34, 1.04) NIV-IPI* 0.83 (0.48, 1.45) ATE+CT, PEM+CT, NIV+IPI+CT, ATE+BEVA+CT, NIV+CT ranked worse than CT. Combination strategies produced more TRAEs of ≥G3, while all ICI monotherapies rank better.	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							SUBPOPULATION BASED ON PD-L1 EXPRESSION **PD-L1 negative (≤ 1%)** Pooled OS (10 trials: 3161 patients) **Pooled HR (95% CI)** *(in comparison to CT)* ICI based treatment 0.79 (0.70, 0.88) **SUCRA RANKING** NIV-IPI 0.41 (0.18, 0.95) NIV-IPI-CT* 0.43 (0.18, 1.00) PEM-CT 0.49 (0.30, 0.79) DURVA-TRE* 0.54 (0.23, 1.25) ATE-BEVA-CT* 0.54 (0.15, 1.94) NIV-CT* 0.61 (0.26, 1.40) ATE-CT 0.61 (0.37, 0.99) Pooled PFS (12 trials: 3214 patients) **Pooled HR (95% CI)** *(in comparison to CT)* ICI based treatment 0.74 (0.69, 0.80) **SUCRA RANKING** ATE-BEVA-CT 0.19 (0.05, 0.69) ATE-CT 0.41 (0.26, 0.67) PEM-CT 0.44 (0.27, 0.71) NIV-IPI-CT* 0.46 (0.20, 1.07) TISLE-CT 0.50 (0.28, 0.91) NIV-CT* 0.54 (0.23, 1.24) NIV-IPI* 0.56 (0.24, 1.31) CAM-CT* 0.58 (0.25, 1.35) **PD-L1 positive (≥ 1%)** Pooled OS (11 trials: 6845 patients) **Pooled HR (95% CI)** *(in comparison to CT)* ICI based treatment 0.83 (0.79, 0.88) **SUCRA RANKING** PEM-CT 0.30 (0.25, 0.97) NIV-IPI-CT* 0.49 (0.15, 1.50) NIV-IPI* 0.56 (0.10, 1.86) PEM* 0.63 (0.21, 2.17) ATE* 0.69 (0.22, 2.21) DURVA* 0.75 (0.24, 2.49) ATE-CT* 0.80 (0.41, 1.57) ATE-BEVA-CT* 0.85 (0.14, 5.01)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							NIV-CT* 0.81 (0.25, 2.59) CT---------- NIVO BEVA-CT Pooled PFS (14 trials: 6281 patients) **Pooled HR (95% CI)** *(in comparison to CT)* ICI based treatment 0.67 (0.58, 0.78) **SUCRA RANKING** PEM-CT 0.18 (0.12, 0.26) ATE-BEVA-CT 0.22 (0.08, 0.36) TISLE-CT 0.25 (0.16, 0.39) CAMRE-CT 0.31 (0.17, 0.59) ATE-CT 0.45 (0.31, 0.64) NIV-IPI-CT 0.45 (0.24, 0.84) ATE * 0.59 (0.32, 1.10) NIVO-IPI * 0.65 (0.36, 1.26) NIVO-CT * 0.69 (0.37, 1.19) BEVA-CT * 0.71 (0.35, 1.46) CT---------- NIVO PEM **PD-L1 1-49% cohort** Pooled OS (10 trials: 2824 patients) **Pooled HR (95% CI)** *(in comparison to CT)* ICI based treatment 0.85 (0.78, 0.93) **SUCRA RANKING** PEM-CT 0.38 (0.20, 0.73) NIV-IPI-CT 0.37 (0.15, 0.95) PEM* 0.84 (0.33, 2.14) NIVO-IPI* 0.89 (0.35, 2.25) ATE-CT* 0.93 (0.54, 1.60) ATE-BEVO-CT* 0.99 (0.24, 4.09) ATE* 1.00 (0.39, 2.54) CT---------- BEVA-CT	

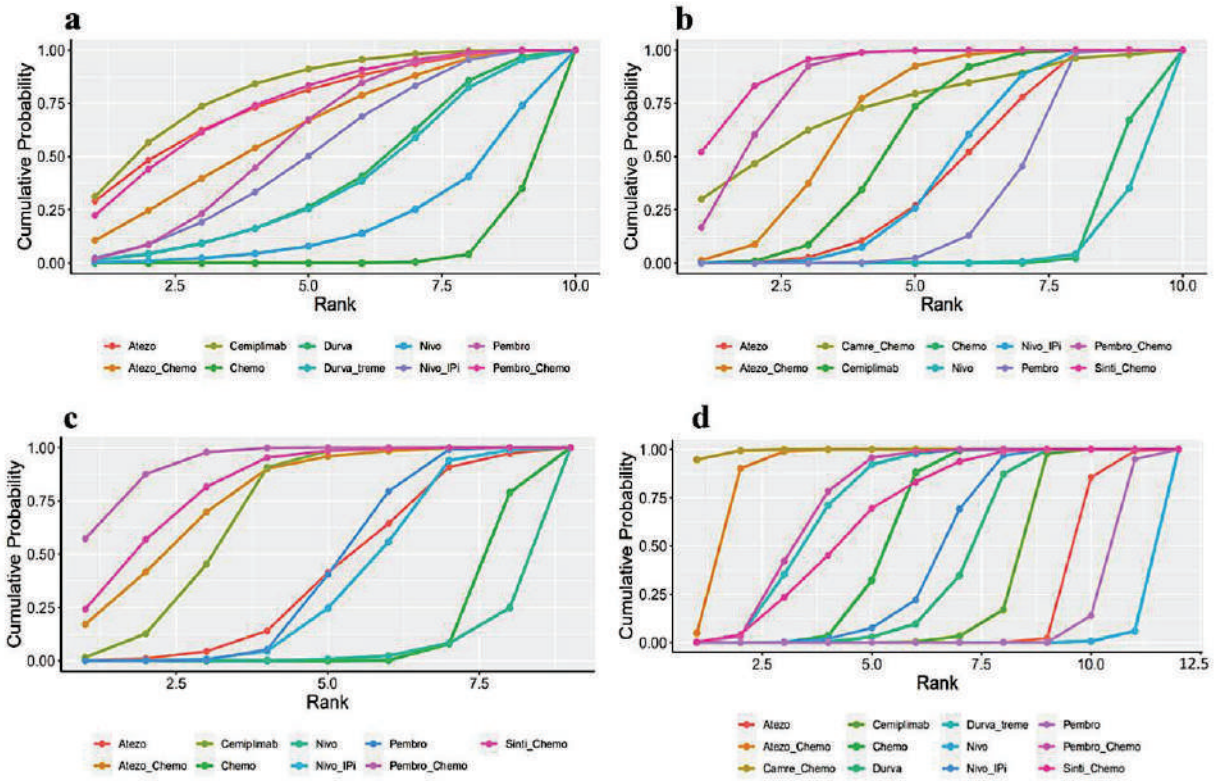
Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							Pooled PFS (12 trials: 2774 patients) **Pooled HR (95% CI)** *(in comparison to CT)* ICI based treatment 0.69 (0.57, 0.84) **SUCRA RANKING** ATE-BEVO-CT* 0.24 (0.04, 1.60) PEM-CT 0.30 (0.12, 0.72) CAM-CT* 0.39 (0.11, 1.34) TISLE-CT* 0.46 (0.19, 1.13) ATE* 0.45 (0.13, 1.57) ATE-CT* 0.49 (0.24, 1.01) NIV-IPI-CT* 0.48 (0.14, 1.67) CT---------- PEM **PD-L1 ≥ 50%** Pooled OS (14 trials: 3536 patients) **Pooled HR (95% CI)** *(in comparison to CT)* ICI based treatment 0.68 (0.62, 0.74) **SUCRA RANKING** CEMI 0.33 (0.14, 0.75) ATEZO 0.35 (0.15, 0.80) PEM-CT 0.38 (0.21, 0.68) ATE-BEVA-CT* 0.36 (0.10. 1.29) PEM 0.44 (0.24, 0.78) ATEZO-CT 0.44 (0.27, 0.72) NIV-IPI-CT 0.45 (0.20, 1.04) NIV-IPI 0.49 (0.22, 1.13) DURVA 0.58 (0.25, 1.33) VURVA-TREME 0.60 (0.25, 1.37) BEVA-CT 0.81 (0.31, 2.11) CT---------- NIV Pooled PFS (16 trials: 3339 patients) **Pooled HR (95% CI)** *(in comparison to CT)* ICI based treatment 0.52 (0.44, 0.62) **SUCRA RANKING** ATE-BEVA-CT 0.06 (0.01, 0.23) PEM-CT 0.13 (0.07, 0.25) TISLE-CT 0.16 (0.08, 0.30) CAM-CT 0.15 (0.06, 0.39)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							ATE-CT 0.21 (0.12, 0.36) CEMI 0.29 (0.12, 0.72) NIV-IPI-CT 0.35 (0.14, 0.87) NIV-IPI 0.39 (0.16, 0.95) ATE 0.40 (0.16, 0.99) PEM 0.42 (0.22, 0.79) CT---------- NIV **AUTHORS' CONCLUSION** - Different ICI treatments rank differently in specific NSCLC cohorts of interest - Regimens with the best outcomes included nivolumab plus ipilimumab with or without chemotherapy for patients with PD-L1 <1%, pembrolizumab plus chemotherapy for those with PD-L1 >1% and 1%–49%, and cemiplimab for those with PD-L1 >50%.	

Evidence Table : **EFFECTIVENESS (IN TREATMENT NAÏVE POPULATION)**
Question : How effective are Immune Checkpoint Inhibitors for the **first line treatment** of PD-L1 positive non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
2. He M, Zheng T, Zhang X, et al. **First-line treatment options for advanced non-small cell lung cancer patients with PD-L1 ≥ 50%: a systematic review and network meta-analysis.** Cancer Immunol Immunother. 2022;71(6):1345-1355.	**Systematic review and network meta-analysis** **Objective** To evaluate the efficacy and toxicity of first-line single-agent ICIs versus ICI combinations for advanced NSCLC patients with PD-L1 ≥ 50%. **Study selection** **Inclusion criteria:** (i) phase 3 RCTs that evaluated the efficacy of first-line ICIs or chemo-ICIs in the treatment of patients with advanced NSCLC; (ii) reported outcomes of overall survival (OS), progression free survival (PFS), objective response rate (ORR) and treatment related adverse events (TRAEs) of grades 3–5; (iii) English was the language of the publication. **Data Source:** PUBMED,EMBASE, Cochrane Library and the Clinicaltrials.gov until December 2020. Individual search of abstract listings from the annual meetings of the American Society of Clinical Oncology (ASCO), the European Society of Medical Oncology (ESMO) and the World Conference of Lung Cancer (WCLC) (2015–2020)	I	14 RCTs involving 3448 patients for advanced NSCLC with PD-L1 ≥ 50%. Keynote 024 Keynote 042 Keynote 407 Keynote 189 IMpower 110 IMpower 130 IMpower 131 IMpower132 CheckMate 227 CheckMate 026 Mystic study EMPOWER-Lung 01 Orient II CAMEL	1. **ICI monotherapy** PEM (2 trials) ATE (1 trial) NIV (1 trial) DURVA (1 trial) CEMI (1 trial) 2. **ICI-chemo** PEM-CT (2 trials) ATE-CT (3 trials) SINTI-CT (1 trial) CAMRE-CT (1 trial) 3. **Dual ICI** NIV-IPI (1 trial) DURVA-TREME (1 trial)	Platinum based-chemotherapy		**OVERALL HIGH PD-L1 POPULATION** **Overall Survival (13 studies)** **Pooled HR (95% CrI)** *(in comparison to CT)* CEMI 0.57 (0.43, 0.77) ATE 0.59 (0.40, 0.87) PEM-CT 0.60 (0.43, 0.83) ATE-CT 0.65 (0.47, 0.71) PEM 0.67 (0.56, 0.80) NIV-IPI 0.70 (0.54, 0.90) DURVA* 0.76 (0.56, 1.0) DURVA-TREME* 0.77 (0.55, 1.1) NIV * 0.90 (0.63, 1.3) - ICIs and ICI combinations showed a significant OS benefit compared to standard chemotherapy. - Cemiplimab provided the best OS benefit versus chemotherapy, followed by ATE and PEM-CT. - Similar efficacies were noted in ATE-CT, PEM and NIV-IPI. - The efficacy of durvalumab showed a boundary significant relationship with chemotherapy. **Progression Free Survival (12 studies)** **Pooled HR (95% CrI)** *(in comparison to CT)* SINTI-CT 0.31 (0.20, 0.49) PEM-CT 0.37 (0.27, 0.49) CAMRE-CT* 0.39 (0.15, 1.0) ATE-CT 0.47 (0.35, 0.63) CEMI 0.54 (0.43, 0.68) NIV-IPI 0.62 (0.49, 0.78) ATE 0.63 (0.45, 0.88) PEM 0.71 (0.60, 0.84) NIV* 1.1 (0.77, 1.5) - Significantly improved PFS was observed in ICIs or ICI combinations	**PEM** = pembrolizumab **ATE** = atezolizumab **NIV** = nivolumab **IPI** = ipilimumab **DURVA** = durvalumab **TREME** = tremelimumab **SINTI** = sintilimab **CAMRE** = camrelizumab **CEMI** = cemiplimab **CT** = chemotherapy * Not statistically significant

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments



Cumulative ranking probability for different treatments. **a** Overall survival; **b** progression free survival; **c** objective response rate; **d** TRAEs of grades 3–5

compared to standard chemotherapy.
- Sinti-CT yielded the best PFS benefit
- PEM-CT showed to be comparable to SINTI-CT in providing PFS benefit.
- Chemo- ICIs were more likely to obtain a greater PFS benefit than single-agent ICIs or dual-agent ICIs.
- The efficacy of CAMRE-CT showed a boundary significant difference
- Nivolumab was likely to show a worse effect than chemotherapy

Objective Response Rate (11 studies)

	Pooled OR (95% CrI) *(in comparison to CT)*
PEM-CT	4.2 (1.7, 6.7)
SINTI-CT	3.4 (1.7, 6.5)
ATE-CT	3.0 (1.5, 6.2)
CEMI	2.5 (1.7, 3.7)
PEM	1.6 (1.2, 2.1)
ATE*	1.6 (0.9, 2.8)
NIV-IPI*	1.5 (1.0, 2.2)
NIV*	0.8 (0.5, 1.4)

- PEM-CT was observed to be the best treatment regarding the objective response (OR: 4.2, 95% CI: 2.6–6.7), which was followed by SINTI-CT and ATE-CT.
- ATE, NIV and NIV-IPI did not show significant benefit in improving ORR over standard chemotherapy,

Grade 3-5 adverse events

	Pooled OR (95% CrI) *(in comparison to CT)*
CAMRE-CT	2.5 (1.7, 3.7)
ATE-CT	1.7 (1.4, 2.1)
PEM-CT*	1.3 (1.0,1.6)
DURVA-TREME*	1.2 (1.0, 1.6)
SINTI-CT*	1.1 (0.8, 1.7)
NIV-IPI*	0.9 (0.7, 1.1)
DURVA*	0.8 (0.6, 1.1)

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							CEMI 0.63 (0.46, 0.85) ATE 0.39 (0.28, 0.55) PEM 0.31 (0.25, 0.39) NIV 0.21 (0.14, 0.32) - The toxicity was found to be lower for the single-agent ICIs across all treatments, and nivolumab (OR: 0.21, 95% CI: 0.14–0.32) was likely to be the lowest. - The addition of chemotherapy to ICIs elevated toxicity compared to standard chemotherapy. - PEM-CT and SINTI-CT were associated with relatively fewer treatment related adverse events of grades 3–5 than the other chemo-ICIs. **SUBGROUP: NON-SQUAMOUS HISTOLOGY** **Overall Survival (5 studies)** **Pooled HR (95% CrI)** *(in comparison to CT)* PEM-CT 0.42 (0.26, 0.68) PEM 0.58 (0.41, 0.83) CEMI 0.64 (0.43, 0.94) ATE-CT 0.81 (0.52, 1.30) - PEM-CT, PEM and CEMI showed a significant benefit in improving OS compared to chemotherapy - PEM-CT was likely to show a better benefit **Progression Free Survival (7 studies)** **Pooled HR (95% CrI)** *(in comparison to CT)* SINTI-CT 0.31 (0.20, 0.49) PEM-CT 0.36 (0.25, 0.52) CAMRE-CT 0.39 (0.15, 1.00) ATE-CT 0.50 (0.35, 0.72) PEM 0.55 (0.39, 0.77) CEMI 0.60 (0.44, 0.82)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							- ATE-CT, CEMI, PEM, PEM-CT and SINTI-CT showed a significant benefit of improving PFS, except CAMRE-CT - SINTI-CT was likely to be the best. **SUBGROUP: SQUAMOUS HISTOLOGY** **Overall Survival (4 studies)** **Pooled HR (95% CrI)** *(in comparison to CT* ATE-CT 0.48 (0.29, 0.80) CEMI 0.48 (0.30, 0.77) PEM 0.73 (0.38, 1.40) PEM-CT 0.79 (0.51, 1.20) CEMI and ATE-CT showed a significant benefit in improving OS compared to chemo- therapy, and their HRs were both 0.48 **AUTHORS' CONCLUSION** - The addition of chemotherapy to ICIs might improve PFS and ORR in advanced NSCLC patients with PD-L1 ≥ 50%. However, there was no OS benefit for chemo-ICIs compared to single-agent ICIs or dual-agent ICIs. In terms of PFS and ORR, pembro-chemo, sinti-chemo and atezo-chemo might be superior choices, while in terms of OS, cemiplimab, atezolizumab and pembro-chemo might be superior choices. - Pembro-chemo and sinti-chemo were likely to have the best benefit of PFS in squamous and non-squamous NSCLC, respectively. In terms of OS, cemiplimab and atezo-chemo showed a similar benefit in improving OS compared to chemotherapy in squamous NSCLC, and pembrolizumab, cemiplimab and pembro-chemo showed a better OS than chemotherapy in non-squamous NSCLC.	

Evidence Table : **EFFECTIVENESS (IN TREATMENT NAÏVE POPULATION)**
Question : How effective are Immune Checkpoint Inhibitors for the **first line treatment** of PD-L1 positive non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
3. Fukuda N, Horita N, Katakura S, Namkoong H, Kaneko A, Somekawa K, Tagami Y, Watanabe K, Hara Y, Kobayashi N, Kaneko T. **The best regimens for chemo-naïve incurable non-squamous non-small cell lung cancer with a programmed death-ligand 1, tumour proportion score 1-49%: a network meta-analysis.** Transl Lung Cancer Res. 2021 Aug;10(8):3550-3566.	**Systematic review and network meta-analysis** **Objective** To assess the efficacy of the ICI regimens in patients with non-squamous NSCLC with low PD-L1 expression and no driver alterations using network meta-analysis. **Study selection** **Inclusion criteria:** **(i)** Eligible treatments included first-line chemotherapy, including cytotoxic agents, molecular targeted therapies, and ICIs. Trials adding angiogenesis inhibitor to the platinum regimen were included. ICIs could be used alone or in combination with platinum regimens. **(ii)** Patients with advanced, locally advanced, or recurrent non-squamous NSCLC with TPS scores of 1–49% were included. **Exclusion criteria:** RCTs examining perioperative chemotherapy and combined chemoradiotherapy were excluded from this study. Patients whose PD-L1 protein expression as determined by the TPS was 50% or higher were excluded. Study focused on patients with squamous NSCLC, driver alterations, or a TPS ≥50%	I	68 eligible studies involving 22,619 patients. **Median age** of patients ranged from 51 years to 67 years **Sample size:** 41 to 1,252, with a median of 248.	Monotherapy or combination therapy with cancer immunotherapy	Platinum based-chemotherapy	Not mentioned	**NON-SQUAMOUS HISTOLOGY** **Overall Survival** - Combination of Pembrolizumab and platinum based chemotherapy (HR =0.55, 95% CI: 0.34–0.89, p=0.015) showed the best OS, followed by the Nivolumab + ipilimumab + platinum based chemotherapy (HR = 0.61, 95% CI: 0.44–0.84, p=0.003) - The OS of the other regimens were not significantly different from that of the platinum based chemotherapy. - Combination of Atezolizumab and chemotherapy (HR =0.70, 95% CI: 0.45–1.08, p=0.110) did not show superiority to the platinum regimen in terms of OS. **Progression Free Survival** **Pooled HR (95% CrI)** *(in comparison to CT)* PEM-CT 0.55 (0.37, 0.81) NIV-CT 0.56 (0.44, 0.72) ATE-CT 0.68 (0.59, 0.80) NIV-IPI* 1.10 (0.86, 1.40) NIV* 1.24 (0.95, 1.61) PEM* 1.24 (0.83, 1.86) - Combination of Pembrolizumab and chemotherapy also showed a high rank in terms of improving PFS. **AUTHORS' CONCLUSION** The addition of Pembrolizumab or Nivolumab plus Ipilimumab to platinum-based chemotherapy seems to be a good therapeutic option for non-squamous NSCLC with a PD-L1 tumour proportion score (TPS) of 1–49%.	

Evidence Table : **EFFECTIVENESS (IN TREATMENT NAÏVE POPULATION)**
Question : How effective are Immune Checkpoint Inhibitors for the **first line treatment** of PD-L1 positive non-small cell lung cancer patients ?

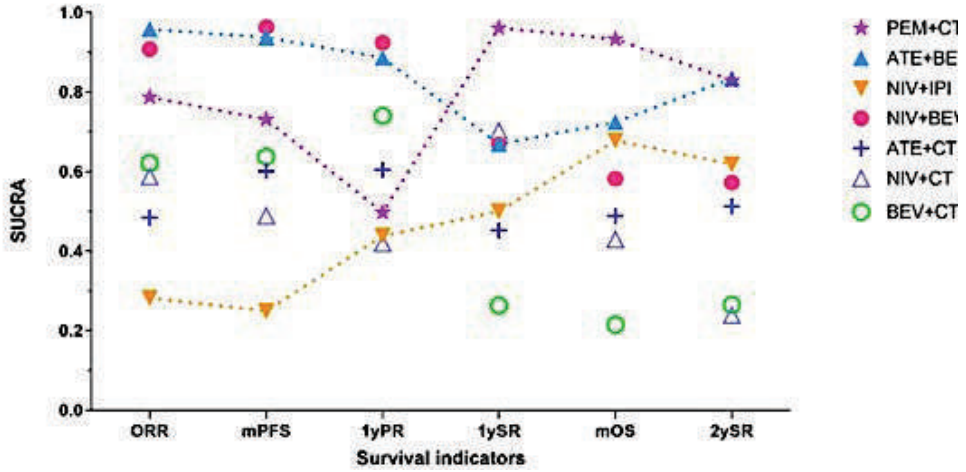
Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
4. Fukuda N, Horita N, Namkoong H, Kaneko A, Somekawa K, Tagami Y, Watanabe K, Hara Y, Kobayashi N, Kaneko T. **Best regimens for treating chemo-naïve incurable squamous non-small cell lung cancer with a programmed death-ligand 1 tumor proportion score of 1%-49%: A network meta-analysis.** Thorac Cancer. 2022 Jan;13(1):84-94.	**Systematic review and network meta-analysis** **Objective** To investigate the efficacy and safety of ICI based regimens in squamous NSCLC with low PD-L1 expression (TPS 1%–49%) and no mutations **Study selection** **Inclusion criteria:** RCTs that enrolled patients with advanced squamous NSCLC and low PD-L1 expression (TPS 1%–49%) with no mutations were included in this study. Studies that included treatment only in the form of first-line chemotherapy **Exclusion criteria:** Trials focusing on non-squamous carcinoma, oncogenic mutations, and patients with a TPS ≥50% were excluded. Studies that included maintenance therapy, second-line therapy, and later-line therapy were excluded.	I	48 studies, which included 16,391 patients **Sample size**: 50 to 1218 with a median of 261 participants. **Average age** of the patients ranged from 51 to 67 years.	ICI administered alone or in combination with platinum-based treatments.	Platinum based-chemotherapy	Not mentioned	**SQUAMOUS HISTOLOGY** (19 studies; 6785 patients) **Overall Survival** **Pooled HR (95% CI)** *(in comparison to CT)* PEM-CT 0.57 (0.36, 0.90) NIV-IPI-CT 0.61 (0.44, 0.84) PEM* 0.87 (0.69, 1.11) IPI-CT* 0.91 (0.77, 1.07) NIV-IPI* 0.97 (0.70, 1.34) ATE-CT* 1.08 (0.81, 1.44) ATE* 1.03 (0.75, 1.42) NIV* 1.20 (0.91, 1.56) Combination of Pembrolizumab and platinum based chemotherapy yielded the best OS benefit compared to chemotherapy (HR = 0.57, 95% CI = 0.36–0.90, p = 0.016), followed by the Nivolumab + Ipilimumab + platinum based chemotherapy) (HR = 0.61, 95% CI = 0.44–0.84, p = 0.003) **Progression Free Survival** **Pooled HR (95% CI)** *(in comparison to CT)* PEM-CT 0.56 (0.32, 0.97) ATE-CT* 0.70 (0.43, 1.14) IPI-CT* 0.87 (0.56, 1.35) NIV-IPI* 1.10 (0.68, 1.78) PEM* 1.24 (0.69, 2.21) NIV* 1.24 (0.76, 2.02) Combination of Pembrolizumab and platinum based chemotherapy showed a significantly lower hazard ratio of progression-free survival than the platinum regimen alone (HR = 0.56, 95% CI = 0.32–0.97, p = 0.040).	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							AUTHORS' CONCLUSION The combination of platinum based chemotherapy and ICIs was the best regimen in terms of OS and PFS, without considerably increasing the risk of adverse events. For squamous lung cancer with PD-L1 TPS of 1%–49%, combination of Atezolizumab and platinum based chemotherapy is recommended by the Guidelines of the American Society of Clinical Oncology, the National Com-prehensive Cancer Network, and the European Society for Medical Oncology. However, in the analysis, the regimen was not significantly different from those of the platinum regimen alone. The platinum-based chemotherapy plus Pembrolizumab and combination of Nivolumab plus Ipilimumab and chemotherapy were considered appropriate first-line agents for treating squamous NSCLC with low PD-L1.	

Evidence Table : **EFFECTIVENESS AND SAFETY (IN TREATMENT NAÏVE POPULATION)**
Question : How effective and safe are Immune Checkpoint Inhibitors for the **first line treatment** of PD-L1 positive non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
5. Zhang X, Xu Q, Yu X et al. **What Is Long-Term Survival and Which First-Line Immunotherapy Brings Long-Term Survival for Advanced Wild-Type Non-Small Cell Lung Cancer: A Network Meta-Analysis Based on Integrated Analysis.** Front Immunol. 2022 Apr;13:764643.	**Systematic review and network meta-analysis** **Objectives** -To determine the best first-line treatment for patients with advanced driver gene-negative NSCLC. -To conduct an integrated analysis of the survival outcomes of RCTs on first- line immuno-related therapies **Study selection** **Inclusion criteria: (i)** Phase II/III RCTs which enrolled previously untreated patients with advanced (stage III/IV or recurrent) histologically confirmed wild-type NSCLC, **(ii)** treated with ICI-containing regimens, and **(iii)** the mOS or 1- or 2-year survival rate with a 95% confidence interval (CI) was available. **Exclusion criteria**: Trials involving targeted therapy for advanced NSCLC with positive driver genes, trials including radiotherapy, cell therapy, vaccine, heat shock protein, and other non-ICI-related therapy.	I	20 RCTs involving 7,462 patients and 16 treatment regimens *KEYNOTE-024* *KEYNOTE-042* *KEYNOTE-021G* *KEYNOTE-189* *KEYNOTE-407* *IMpower-110* *IMpower-130* *IMpower-131* *IMpower-132* *IMpower-150* *CheckMate-026* *CheckMate-227* *CheckMate-9LA* *EMPOWER-LUNG1* *CAMEL* *Lynch* *Govindan* *MYSTIC* *CCTG BR.34* *2020ESMOLBA54* **Phase II trial** 2 studies **Phase III trial** 18 studies Majority open label **Sample size:** 60-637 **Median age of participants :** 59-66 years old	**1. ICI monotherapy** - PEM *(2 studies)* - ATE (*1 study*) - NIV (*1 study*) - DUR (*1 study*) - CEM (*1 study*) **2. ICI-Chemo** - PEM+CT (*3 studies*) - ATE+CT (*3 studies*) - NIV+CT (1 study) - IPI+CT *(2 studies*) - CAM+CT (*1 study*) **3. Dual ICI** - NIV+IPI (*1 study*) - DUR+TRE (*1 study*) **4. Dual ICI-Chemo** -NIV+IPI+CT (*1 study*) -DUR+TRE+CT (*1 study*) **5. ICI-AA-Chemo** - ATE+BEV+CT (*1 study*) - NIV+BEV+CT (*1 study*)	Platinum based-chemotherapy	Median 12-60 months	**OVERALL POPULATION** **1. SPECIFIC TREATMENT STRATEGIES** **OS** **Pooled mOS (95%CI) (months)** ICI based treatment 16.20 (14.79, 17.60) - ICI monotherapy (5 studies) 15.41 (12.73, 18.09) - Single ICI-CT (9 studies) 16.82 (14.71, 18.93) - Dual ICI (3 studies) 14.08 (10.00, 18.15) - Dual ICI-CT (2 studies) 16.07 (13.84, 18.29) - ICIs-BEV-CT (1 study) 19.50 (16.90, 22.10) **1-year Survival Rate** **Pooled Odd Ratios(95%CI)** ICI based treatment 0.63 (0.59, 0.66) - ICI monotherapy (6 studies) 0.60 (0.54, 0.67) - Single ICI-CT (11 studies) 0.64 (0.60, 0.68) - Dual ICI (3 studies) 0.55 (0.45, 0.65) - Dual ICI-CT (2 studies) 0.62 (0.58, 0.68) - ICIs-BEV-CT (2 studies) 0.74 (0.61, 0.87) **2-year Survival Rate** **Pooled Odd Ratios(95%CI)** ICI based treatment 0.37 (0.33, 0.41) - ICI monotherapy (6 studies) 0.38 (0.30, 0.46) - Single ICI-CT (10 studies) 0.36 (0.30, 0.42) - Dual ICI (2 studies) 0.35 (0.25, 0.45) - Dual ICI-CT (3 studies) 0.33 (0.17, 0.49) - ICIs-BEV-CT (2 studies) 0.37 (0.33, 0.41) **2. SPECIFIC TREATMENT REGIMENS** **OS** **Pooled mOS (95%CI) (months)** PEM 19.85 (10.60, 29.10) NIV 14.40 (11.55, 17.25) ATE 17.50 (12.35, 22.65) PEM-CT 19.54 (14.73, 24.34) ATE-CT 17.22 (18.43,19.16) NIV-CT 18.30 (15.50, 21.10) NIV-IPI 17.10 (14.75,19.45) DUR-TRE 12.11 (9.47, 14.76) NIV-IPI-CT 15.60 (12.55,18.65) ATE-BEV-CT 19.50 (16.90, 22.10) DUR-TRE-CT 16.60 (13.35,19.85)	**ICI** = Immunotherapy **CT** = Chemotherapy **AA**=Anti-angiogenesis **BEV**= Bevacizumab **PEM**= Pembrolizumab **ATE**= Atezolizumab **NIV**= Nivolumab **DUR**= Durvalumab **TRE**= Tremelimumab **CAM**= Camrelizumab **CEM**= Cemiplimab **IPI**= Ipilimumab **BEV**= Bevacizumab * Not statistically significant

Bibliographi Citation	Study Type/ Methods		Number of Patients & Patient Characterist	Intervention	Comparison	Length of Follow Up (If pplicable)	Outcome Measures/ Effect Size	eneral Comment
	A network meta-analysis (NMA) based on the Bayesian model was performed to compare and rank these treatment regimens with **long-term survival** according to						nost all immuno-related therapies significantly onged OS compared with CT. **Pooled HR(95%CI)** **RA RANKING** (*in comparison to CT*) M-CT 0.62 (0.54, 0.72) -CT 0.79 (0.69, 0.90) -IPI 0.73 (0.64, 0.84) M-CT 0.72 (0.52, 1.00) -BEV-CT * 0.75 (0.53, 1.06) -CT 0.79 (0.69, 0.90) -CT 0.81 (0.76, 0.97) M 0.82 (0.72, 0.94) * 0.83 (0.65, 1.07) -CT * 0.88 (0.75, 1.04) **EM+CT** (relative to CT) ranked first in mOS, wed by **ATE+BEV+CT** and the third was the **+IPI**. e OS of **PEM+CT** was prolonged significantly pared to **NIV+CT** [HR 0.77(95%CI 0.61, 0.97)] **ATE+CT** [HR 0.79 (95%CI 0.65, 0.96)] **lian Progression-Free Survival (mPFS)** **Pooled HR(95%CI)** **RA RANKING** (*in comparison to CT*) -BEV-CT 0.31 (0.23, 0.42) -BEV-CT 0.33 (0.26, 0.42) M-CT 0.53 (0.46, 0.60) -CT 0.56 (0.48, 0.66) -CT 0.57 (0.51, 0.64) M-CT 0.61 (0.46, 0.80) -CT 0.62 (0.52, 0.74) 0.77 (0.63, 0.94) -IPI 0.79 (0.69, 0.91) M* 1.05 (0.93, 1.19) he top three rankings of SUCRA cumulative bability were **NIV+BEV+CT, ATE+BEV+CT** and **M+CT**	



SUCRA value of efficacy ranking probability of main immuno-related therapies for advanced NSCLC

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							1-year Survival Rate in overall population - Except for ATE, CAM+CT, and NIV+BEV+CT, almost all immuno-related treatments have significantly improved 1ySR compared to CT alone. **SUCRA RANKING** — **Pooled ORs(95%CI)** *(in comparison to CT)* PEM-CT 2.12 (1.68, 2.67) NIV-IPI 1.38 (1.10, 1.75) NIV-BEV-CT* 1.59 (0.96, 2.62) ATE-BEV-CT 1.55 (1.10, 2.19) CAM-CT* 1.48 (0.97, 2.28) NIV-IPI 1.38 (1.10, 1.75) ATE-CT 1.35 (1.09, 1.67) PEM 1.32 (1.05, 1.64) BEV-CT* 1.20 (0.90, 1.60) ATE * 1.16 (0.83, 1.62) - The 1ySR of PEM-CT was improved significantly compared to ATE-CT (OR 1.57, 1.15~2.15) and NIV-IPI (1.53, 1.10~2.12). **1-year Progression-Free Survival Rate in overall population** - PEM-CT, ATE-CT, ATE-BEV-CT, NIV-BEV-CT, and BEV-CT were significantly higher than that of CT **SUCRA RANKING** — **Pooled ORs(95%CI)** *(in comparison to CT)* NIV-BEV-CT 11.11 (2.25, 78.06) ATE-BEV-CT 8.72 (2.23, 42.81) BEV-CT 4.81 (2.05, 15.60) ATE-CT 3.40 (1.44, 9.01) PEM-CT 2.65 (1.11, 6.17) NIV-IPI* 2.32 (0.54, 9.74) ATE* 2.24 (0.51, 9.71) NIV-CT* 2.21 (0.53, 9.36) CAM-CT* 1.72 (0.39, 7.46) PEM* 1.08 (0.25, 4.69)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							2-year Survival Rate in overall population - The top three cumulative probabilities of SUCRA were ATE-BEV-CT (versus CT), PEM-CT, and PEM **SUCRA RANKING** — **Pooled ORs(95%CI)** *(in comparison to CT)* ATE-BEV-CT: 1.80 (1.29, 2.52) PEM-CT: 1.79 (1.41, 2.27) PEM: 1.67 (1.32, 2.11) NIV-IPI: 1.55 (1.22, 1.98) NIV-BEV-CT*: 1.51 (0.98, 2.32) ATE-CT: 1.46 (1.17, 1.81) ATE*: 1.31 (0.92, 1.87) BEV-CT*: 1.24 (0.95, 1.64) NIV-CT*: 1.19 (0.89, 1.60) **OBJECTIVE RESPONSE RATE** **SUCRA RANKING** — **Pooled ORs(95%CI)** *(in comparison to CT* ATE-BEV-CT: 4.12 (2.91, 5.84) NIV-BEV-CT: 3.67 (2.33, 5.76) PEM-CT: 3.15 (2.43, 4.08) NIV-CT: 2.46 (1.83, 3.32) CAM-CT: 2.34 (1.58, 3.51) ATE-CT: 2.14 (1.72, 2.68) NIV-IPI: 1.29 (1.00, 1.65) PEM*: 1.04 (0.81, 1.33) ATE*: 0.89 (0.62, 1.28) **≥ GRADE 3 ADVERSE EVENTS** **SUCRA RANKING** — **Pooled ORs(95%CI)** *(in comparison to CT* ATE-BEV-CT: 3.00 (2.15, 4.19) NIV-BEV-CT: 2.13 (1.32, 3.44) CAM-CT: 2.00 (1.34, 3.00) ATE-CT: 1.71 (1.38, 2.13) NIV-CT: 1.52 (1.13, 2.05) PEM-CT*: 1.25 (0.97, 1.63) NIV-IPI*: 0.87 (0.68, 1.11) PEM: 0.31 (0.24, 0.41) ATE: 0.19 (0.12, 0.28)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments

	Overall population					Non-squ	Squ	PD-L1≥50% TC/IC=3			High-TMB
Treatment	OS	ORR	≥3AEs	1yOR	2yOR	OS	OS	OS	1yOR	2yOR	OS
PEM+CT	1	3	7	1	2	1	2	2	1	5	4
ATE+BEV+CT	2	1	1	4	1	2	NA	NA	NA	NA	NA
NIV+IPI	3	8	9	6	4	6	NA	7	6	6	2
CAM+CT	4	6	3	5	NA	3	NA	NA	NA	NA	NA
NIV+BEV+CT	5	2	2	3	5	4	NA	NA	NA	NA	NA
ATE+CT	6	7	5	7	6	5	NA	4	7	7	NA
NIV+CT	7	5	6	2	9	7	1	NA	NA	NA	NA
PEM	8	9	10	8	3	NA	NA	6	4	3	1
ATE	9	11	11	10	7	NA	NA	3	5	2	7
BEV+CT	10	4	4	9	8	8	NA	NA	NA	NA	NA
CT	11	10	8	11	10	9	3	10	9	9	8
CEM	NA	NA	NA	NA	NA	NA	NA	1	2	1	NA
NIV+IPI+CT	NA	NA	NA	NA	NA	NA	NA	5	3	4	NA
DUR	NA	NA	NA	NA	NA	NA	NA	8	NA	NA	3
NIV	NA	NA	NA	NA	NA	NA	NA	9	8	8	9
DUR+TRE	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	5
DUR+TRE+CT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6

	Overall population				Non-squ	Squ	PD-L1≥50% TC/IC=3		High-TMB
Treatment	PFS	ORR	≥3AEs	1yPR	PFS	PFS	PFS	1yPR	PFS
NIV+BEV+CT	1	2	2	1	1	NA	NA	NA	NA
ATE+BEV+CT	2	1	1	2	2	NA	NA	NA	NA
PEM+CT	3	3	7	5	3	2	1	2	1
BEV+CT	4	4	4	3	4	NA	NA	NA	NA
ATE+CT	5	7	5	4	5	NA	2	4	NA
CAM+CT	6	6	3	9	6	NA	NA	NA	NA
NIV+CT	7	5	6	8	7	1	NA	NA	NA
ATE	8	11	11	7	NA	NA	5	7	3
NIV+IPI	9	8	9	6	NA	NA	4	3	2
CT	10	10	8	11	8	3	8	8	8
PEM	11	9	10	10	NA	NA	6	6	NA
CEM	NA	NA	NA	NA	NA	NA	3	1	NA
NIV	NA	NA	NA	NA	NA	NA	7	5	4
DUR+TRE+CT	NA	NA	NA	NA	NA	NA	NA	NA	5
DUR	NA	NA	NA	NA	NA	NA	NA	NA	6
DUR+TRE	NA	NA	NA	NA	NA	NA	NA	NA	7

The probability of the ranking of each treatment on survival indicators for overall population and subgroups

SUBPOPULATION BASED ON PD-L1 EXPRESSION

HIGH PD-L1 EXPRESSION (PD-L1 ≥50%)

Overall Survival

SUCRA RANKING	**Pooled HR (95%CI)** *(in comparison to CT)*
CEM	0.57 (0.42, 0.77)
PEM-CT	0.59 (0.40, 0.86)
ATE	0.60 (0.40, 0.89)
ATE-CT	0.65 (0.47, 0.91)
NIV-IPI-CT	0.66 (0.44, 0.99)
PEM	0.67 (0.57, 0.78)
NIV-IPI	0.70 (0.55, 0.90)

Progression Free Survival

SUCRA RANKING	**Pooled HR(95%CI)** *(in comparison to CT)*
PEM-CT	0.35 (0.11, 1.10)
ATE-CT	0.46 (0.20, 1.06)
CEM	0.54 (0.18, 1.66)
NIV-IPI	0.62 (0.20, 1.91)
ATE	0.63 (0.20, 2.00)
PEM	0.65 (0.29, 1.43)
NIV	0.75 (0.24, 2.31)

1-year Survival Rate

SUCRA RANKING	**Pooled ORs(95%CI)** *(in comparison to CT)*
PEM-CT	2.95 (1.62, 5.44)
CEM	2.25 (1.59, 3.21)
NIV-IPI-CT	2.23 (1.21, 4.18)
PEM	1.80 (1.38, 2.35)
ATE	1.75 (1.00, 3.09)
NIV-IPI	1.71 (1.14, 2.58)
ATE-CT	1.41 (1.05, 1.91)
NIV*	1.34 (0.90, 1.99)

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							2-year Survival Rate **SUCRA RANKING** — **Pooled ORs(95%CI)** *(in comparison to CT)* CEM — 2.75 (1.94, 3.93) ATE — 2.54 (1.40, 4.71) PEM — 1.96 (1.49, 2.57) NIV-IPI-CT — 1.83 (1.00, 3.36) PEM-CT* — 1.65 (0.92, 3.01) NIV-IPI — 1.63 (1.09, 2.45) ATE-CT — 1.62 (1.18, 2.46) NIV — 1.30 (0.87, 1.94) **AUTHORS' CONCLUSION** Atezolizumab combined with bevacizumab and chemotherapy or **pembrolizumab plus chemotherapy** are likely to bring the longest LS in the overall population, while **single ICI** may be adequate for patients with a high PD-L1 expression. ICIs with bevacizumab and chemotherapy may be the best combination for LS for its further advantage over time.	

Evidence Table : **EFFECTIVENESS AND SAFETY (IN PRE-TREATED POPULATION)**
Question : How effective and safe are Immune Checkpoint Inhibitors **as second and/or further lines treatment options** for PD-L1 positive advanced non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
6. Passiglia F, Galvano A, Rizzo S, Incorvaia L, Listì A, Bazan V, Russo A. **Looking for the best immune-checkpoint inhibitor in pre-treated NSCLC patients: An indirect comparison between nivolumab, pembrolizumab and atezolizumab.** Int J Cancer. 2018 Mar 15;142(6):1277-1284. doi: 10.1002/ijc.31136. Epub 2017 Nov 14. PMID: 29080213.	**Systematic review and meta-analysis** **Objective** To assess any difference in both efficacy and safety profiles among Nivolumab, Pembrolizumab and Atezolizumab in pre-treated NSCLC patient **Study selection** **Inclusion criteria:** **(i)** patients with histologically proven diagnosis of NSCLC **(ii)** patients who failed prior platinum chemotherapy regimens **(iii)** studies comparing single agent anti-PD1/PDL1 MoAb versus docetaxel **(iv)** studies reporting efficacy outcomes, including ORR, PFS, OS; **(v)** studies reporting safety outcomes, including Grade 3–5 adverse events (G3–G5 AEs), pneumonitis and discontinuation rate. **Exclusion criteria:** Ongoing studies and observational trials	I	5 RCTs included *CheckMate017* *CheckMate057* *KEYNOTE010 (2mg/kg)* *KEYNOTE010 (10mg/kg)* *POPLAR* *OAK* * KEYNOTE-010 trial of pembrolizumab included only patients with a threshold level of tumour PD-L1 expression >1%	ICI - Nivolumab *(2 studies)* - Pembrolizumab *(1 study)* - Atezolizumab *(2 studies)*	Docetaxel (standard second-line chemotherapy regimen)	Up to 2 years	**EFFECTIVENESS - DIRECT COMPARISON** **1. Overall population** *Nivolumab versus docetaxel* **Pooled HR (95% CI)** OS 0.68 (0.57, 0.80) PFS 0.77 (0.52, 1.13) **Pooled RR (95% CI)** ORR 1.68. (1.21, 2.34) *Pembrolizumab versus docetaxel* * **Pooled HR (95% CI)** OS 0.66 (0.57, 0.77) PFS 0.83 (0.74, 0.94) **Pooled RR (95% CI)** ORR 1.96 (1.48, 2.59) *Atezolizumab versus docetaxel* **Pooled HR (95% CI)** OS 0.73 (0.63. 0.85) PFS 0.95 (0.83, 1.08) **Pooled RR (95% CI)** ORR 1.01 (0.76, 1.35) **2. PD-L1 positive (≥ 1%) population** *Nivolumab versus docetaxel* **Pooled HR (95% CI)** OS 0.62 (0.48, 0.81) PFS 0.69 (0.55, 0.87) **Pooled RR (95% CI)** ORR 2.26 (1.42, 3.61) *Pembrolizumab versus docetaxel* **Pooled HR (95% CI)** OS 0.66 (0.57, 0.77) PFS 0.83 (0.74, 0.94) **Pooled RR (95% CI)** ORR 1.96 (1.48, 2.50) *Atezolizumab versus docetaxel* **Pooled HR (95% CI)** OS 0.69 (0.57, 0.85) PFS 0.89 (0.75, 1.06)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							Pooled RR (95% CI) ORR 1.09 (0.80, 1.49) **3. PD-L1 negative (≤ 1%) population** *Nivolumab versus docetaxel* **Pooled HR (95% CI)** OS 0.68 (0.57, 0.80) PFS 0.97 (0.76, 1.25) **Pooled RR (95% CI)** ORR 0.90 (0.50, 1.62) *Atezolizumab versus docetaxel* **Pooled HR (95% CI)** OS 0.73 (0.63, 0.85) PFS 1.02 (0.84, 1.25) **Pooled RR (95% CI)** ORR 0.75 (0.46, 1.23) **EFFECTIVENESS - INDIRECT COMPARISON** **PD-L1 positive (≥ 1%) population** *Nivolumab versus Pembrolizumab* **Pooled HR (95% CI)** OS 0.94 (0.69, 1.27) PFS 0.83 (0.64, 1.08) **Pooled RR (95% CI)** ORR 1.15 (0.67, 1.99) *Nivolumab versus Atezolizumab* **Pooled HR (95% CI)** OS 0.90 (0.65, 1.25) PFS 0.77 (0.58, 1.03) **Pooled RR (95% CI)** ORR 2.07 (1.18, 3.63) *Pembrolizumab versus Atezolizumab* **Pooled HR (95% CI)** OS 0.96 (0.75, 1.23) PFS 0.93 (0.76, 1.15) **Pooled RR (95% CI)** ORR 1.80 (1.18, 2.73)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							SAFETY OUTCOMES – DIRECT COMPARISON **1. Grade 3-4 Adverse Events** **Pooled RR (95% CI)** *Nivolumab versus docetaxel* 0.17 (0.13, 0.24) *Pembrolizumab versus docetaxel* 0.41 (0.33, 0.50) *Atezolizumab versus docetaxel* 0.34 (0.28, 0.41) **2. Discontinuation rate** **Pooled RR (95% CI)** *Nivolumab versus docetaxel* 0.48 (0.25, 0.94) *Pembrolizumab versus docetaxel* 0.50 (0.23, 1.05) *Atezolizumab versus docetaxel* 0.39 (0.23, 0.64) **3. Pneumonitis** **Pooled RR (95% CI)** *Nivolumab versus docetaxel* 9.22 (1.73, 49.10) *Pembrolizumab versus docetaxel* 2.34 (1.21, 4.52) *Atezolizumab versus docetaxel* 8.77 (1.12,68.92) **SAFETY OUTCOMES – INDIRECT COMPARISON** **1. Grade 3-4 Adverse Events** **Pooled RR (95% CI)** *Nivolumab versus Pembrolizumab* 0.41 (0.29, 0.60) *Nivolumab versus Atezolizumab* 0.50 (0.35, 0.72) *Pembrolizumab versus Atezolizumab* 1.21 (0.91, 1.60) **2. Discontinuation rate** **Pooled RR (95% CI)** *Nivolumab versus Pembrolizumab* 0.96 (0.35, 2.83) *Nivolumab versus Atezolizumab* 1.23 (0.53, 2.84) *Pembrolizumab versus Atezolizumab* 1.28 (0.51, 3.20)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							3. Pneumonitis **Pooled RR (95% CI)** *Nivolumab versus Pembrolizumab* 3.94 (0.85, 23.79) *Nivolumab versus Atezolizumab* 1.05 (0.07, 14.93) *Pembrolizumab versus Atezolizumab* 0.27 (0.03, 2.32) **AUTHORS' CONCLUSION** - None of the three ICIs was statistically superior in terms of both PFS and OS. - A significant increase in ORR with both the anti PD1 MoAb nivolumab and pembrolizumab as compared to the anti-PDL1 atezolizumab in the overall population and in PDL1-positive patients, while no activity differences between nivolumab and pembrolizumab have been observed. - Significant lower incidence of all Grade 3–5 AEs during nivolumab therapy as compared with both pembrolizumab and atezolizumab treatments. - Even if it is not statistically significant, pembrolizumab has shown to be most tolerated agent, since it was associated with the lower incidence of autoimmune pneumonitis as compared with the other two checkpoint inhibitors.	

Evidence Table : **EFFECTIVENESS (IN PRE-TREATED POPULATION)**
Question : How effective are Immune Checkpoint Inhibitors **as second and/or further lines treatment options** for PD-L1 positive advanced non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
7. Juarez-Garcia A, Sharma R, Hunger M, Kayaniyil S, Penrod JR, Chouaïd C. **Real-world effectiveness of immunotherapies in pre-treated, advanced non-small cell lung cancer Patients: A systematic literature review.** Lung Cancer. 2022 Mar; 166:205-20.	**Systematic review and meta-analysis** **Objective** To systematically review the existing real-world evidence (RWE) on the survival outcomes of immune-oncologic agents in second- or higher line in advanced NSCLC. **Study selection** **Inclusion criteria** **(i)** Studies that included adults (18 years of age and older) who were previously treated with first-line anti-cancer therapy for locally advanced (stage IIIB or IIIC), metastatic (stage IV) or recurrent NSCLC. **(ii)** The sample size of the overall study population was to be ≥ 60, to allow for more generalizable real-world findings, however the subpopulations of interest for which OS was reported, could have a sample size lower than 60. **(iii)** Studies that additionally comprised patients receiving IO treatment in the first-line were included only if this patient group constituted ≤ 10% of the study population. **(iv)** Studies had to have at least reported OS to be eligible for inclusion. Search for peer-reviewed publications included studies published between	I	66 included studies comprising 57,016 pre-treated, advanced NSCLC patients. 57 single-arm observational studies and nine comparative effectiveness studies. **Study settings** USA 21% France 15% Netherlands 3% Australia 3% Italy 10% Portugal 1.5% Israel 4.5% Japan 7.5% Russia 1.5% Korea 1.5% China 3.0% Spain 9.0% Canada. 3.0% Denmark 1.5% Germany 3.0% Australia 4.5% Czech Republic 1.5% **Sample size** : 61 - 10,689 **Characteristics of studied participants** 1. Median age range: 58-74 years old 2. Male 43% - 80% 3. Current or former smokers 40.3% - 92.3% 4. PD-L1 status (19 studies) Positive 0.5 – 100% Negative 0.7 - 41.5% 5. ECOG Performance Status (46 studies) ECOG ≥2 43 studies	1. Nivolumab (55 studies) 2. Pembrolizumab (10 studies) 3. Atezolizumab (1 studies)	No comparator or each other or chemotherapy	Median follow-up time ranged from 3.5 to 26.1 months.	**OVERALL POPULATION** **1. Nivolumab monotherapy** (47 studies) Median OS 4.2 – 17 months Pooled 1-year OS rate 45.6% (95% CI; 43.4–47.8) Pooled 2-year OS rate 28% (95% CI; 24.8–31.4) **2. Pembrolizumab monotherapy** (1 study) Median OS 13.5 months 1-year OS rate 53.6% 2-year OS rate Not reported **3. Atezolizumab monotherapy** (1 study) Median OS 6.5 months 1-year OS rate 34.6% 2-year OS rate Not reached **4. Non-ICI group** (best supportive care, chemotherapy, sequential targeted treatment) Median OS 1.1 months (best supportive care) - 29.3 months (sequential targeted treatment) Pooled 1-year OS rate 30.2% (95% CI; 20.6–41.9) Pooled 2-year OS rate 23.9% (95% CI; 19.8–28.4) **SUBPOPULATION** **Histological Type** (Nivolumab) **1. Squamous histology** (8 studies) Median OS 5.5 – 15.5 months Pooled 1-year OS rate 41.8% (95% CI; 34.9 – 49.0) Pooled 2-year OS rate 24.7% (95% CI; 18.1 – 32.6) **2. Non-squamous histology** (9 studies) Median OS 5.8 – 19.3 months Pooled 1-year OS rate 46.6% (95% CI; 43.1– 50.1) Pooled 2-year OS rate 32.2% (95% CI; 27.0 – 37.9)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
	January 1, 2015 and August 28, 2019		ECOG ≤2. 3 studies ECOG 0 7 – 90.8% ECOG 1 21.2 – 82.0% ECOG 2 7 – 35.3% ECOG 3 1.6 – 32.3% ECOG 4 0.1 - 17.2% 6. CNS metastases (31 studies) 5 – 40% 7. Liver metastases (16 studies) 10 – 39%				Pooled estimates for other treatment groups by histology were not calculated due to having < 3 estimates. **PDL1 status** (4 studies – Nivolumab) **1. Positive** Median OS 8.2 – 18.1 months Pooled 1-year OS rate 46.3% (95% CI; 34.2– 59.0) Pooled 2-year OS rate Not calculated (insufficient number of estimates) **2. Negative** Median OS 5.5 – 9.1 months Pooled 1-year OS rate 27.8% (95% CI; 21.9 – 34.5) Pooled 2-year OS rate Not calculated (insufficient number of estimates) Pooled estimates for other treatment groups by PD-L1 status were not calculated because of an insufficient number of estimates. **Elderly population** (8 studies – Nivolumab) **1. ≥ 75 years old** Median OS 4.7 – 12.1 months Pooled 1-year OS rate 39.6% (95% CI; 34.8 – 44.6) Pooled 2-year OS rate 21.3% (95% CI; 17.0 – 26.4) **2. < 75 years old** Median OS 6.3 – 15.5 months Pooled 1-year OS rate 43.2% (95% CI; 39.4 –47.1) Pooled 2-year OS rate 25.5% (95% CI; 19.9 –32.1) * Pooled estimates for other treatment groups by age were not calculated because of an insufficient number of estimates. **ECOG performance status** (15 studies – Nivolumab) **1. ECOG ≥ 2** Median OS 2.6 – 7.0 months Pooled 1-year OS rate 27.1% (95% CI; 17.8 – 39.0) Pooled 2-year OS rate Not calculated (insufficient number of estimates) **2. ECOG < 2** Median OS 7.3 – 15.5 months	

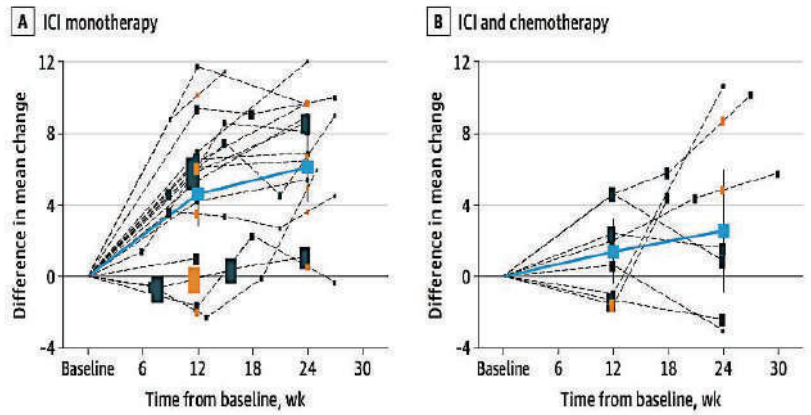
Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							Pooled 1-year OS rate 51.6% (95% CI; 44.4 – 58.8) Pooled 2-year OS rate 26.4% (95% CI; 21.4 – 32.1) No study that assessed pembrolizumab monotherapy or atezolizumab monotherapy reported survival by ECOG PS. **CNS metastases** (11 studies – Nivolumab) **1. Present** Median OS 3.1 – 14.8 months Pooled 1-year OS rate 41.9% (95% CI; 38.7 – 45.2) Pooled 2-year OS rate 22.1% (95% CI; 13.4 – 34.2) **2. Absent** Median OS 5.1 – 13.1 months Pooled 1-year OS rate 40.0% (95% CI; 33.9 – 46.3) Pooled 2-year OS rate 26.1% (95% CI; 19.3 – 34.2) Pooled estimates for other treatment groups by presence of CNS metastases were not calculated because of an insufficient number of estimates. **Liver metastases** (4 studies - Nivolumab) **1. Present** Median OS 3.6 – 7.5 months Pooled 1-year OS rate 23.8% (95% CI; 14.9 - 35.7) Pooled 2-year OS rate Not reached **2. Absent** Median OS 5.8 – 20.7 months Pooled 1-year OS rate 43.4% (95%CI; 34.4 - 52.9) Pooled 2-year OS rate Not calculated (insufficient number of estimates) **AUTHORS' CONCLUSION** Most of the evidence base reported on nivolumab treatment (55 of the 66 studies containing nivolumab treatment), which was anticipated considering it was the first immunotherapy agent to be approved for this indication, with an early access program in several countries. Pooled estimates of 1-year and 2-year OS rate associated with nivolumab treatment in RWE studies indicates that the survival benefits of nivolumab treatment can be seen in previously treated patients	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							with locally advanced or metastatic NSCLC in the real-world setting. Patients with tumours expressing PD-L1 have been shown to have better survival outcomes associated with IO compared to PD-L1 negative patients. No significant difference in survival between elderly and non-elderly patients. Poor performance status is associated with shorter survival outcomes for nivolumab.	

Evidence Table : **EFFECTIVENESS (PATIENT REPORTED OUTCOMES)**
Question : How effective are Immune Checkpoint Inhibitors for PD-L1 positive advanced non-small cell lung cancer patients in improving health-related quality of life ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
8. Pala L, Sala I, Oriecuia C, et al. **Association of Anticancer Immune Checkpoint Inhibitors With Patient-Reported Outcomes Assessed in Randomized Clinical Trials: A Systematic Review and Meta-analysis**. JAMA Netw Open. 2022;5(8):e2226252.	**Systematic review and meta-analysis** **Objective** To evaluate patient-reported outcomes (PROs) assessed in RCTs of immunotherapy-based treatments. **Study selection** **Inclusion criteria:** - RCTs that assessed programmed cell death receptor 1, programmed cell death ligand 1 (PD-L1), and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitors as monotherapy or in combination with another ICI and/or other anticancer drugs (ie, targeted therapy or chemotherapy) vs control groups not containing immunotherapy in patients with advanced solid tumours. - Trials in which PROs were assessed through the Global Health Status (GHS) scale from the European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life Questionnaire (QLQ-C30) or the EuroQol Health-Related Quality of Life 5-Dimension, 3-Level (EQ-5D-3L) visual analogue scale (VAS). **Exclusion criteria:** - Single-group phase 1 and 2 trials and RCTs conducted in adjuvant and neoadjuvant settings or in hematologic	I	34 RCTs involving 18,709 patients - 21 studies investigated PROs in the first-line setting - 13 studies explored PROs in lines beyond first - 19 trials tested ICIs as monotherapy - 8 trials evaluated the combination of ICIs with chemotherapy - 8 trials tested other ICIs-containing combinations.	PD-1/PD-L1/CTLA-4 inhibitors as monotherapy or in combination with another ICI and/or other anticancer drugs (ie, targeted therapy or chemotherapy) 1. anti-PD1 or anti–PD-L1 monotherapy (19 trials) 2. anti-PD1 or anti–PD-L1 combined with chemotherapy (8 trials) 3. anti-PD1 or anti–PD-L1 drug combined with targeted therapy (3 trials) 4. combination of an anti-PD1 with an anti-CTLA4 drug (3 trials)	Control groups not containing immunotherapy	-	**Outcome measures** (1) the difference in mean change of PRO scores between treatment groups at 12 weeks from baseline (2) the differences in mean change of PRO scores between treatment groups at 24 weeks from baseline (3) the hazard ratio (HRs) for time to deterioration (TTD) in PROs. **MEAN CHANGE OF PRO SCORES BETWEEN TREATMENT GROUPS AT 12 WEEKS AND 24 WEEKS FROM BASELINE** **ICI monotherapy (19 trials)** - Mean change of PRO score from baseline to 12 and 24 weeks of follow-up was reported in 16 trials and 14 trials, respectively - PRO score was assessed by the EORTC QLQ-C30 GHS in 13 trials and by the EQ-5D-3L VAS in 3 trials. - The pooled between-groups difference of mean change in PRO score from baseline was 4.6 (95% CI 2.8-6.4) at week 12 and 6.1 (95% CI 4.2-8.1) at week 24, favouring ICI monotherapy **ICI in combination with chemotherapy (8 trials)** - Mean change in PRO score from baseline to 12 and 24 weeks of follow-up was reported in all 8 trials at 12 weeks and 7 trials at 24 weeks - PRO score was assessed by the EORTC QLQ-C30 GHS in all the trials - The pooled between- groups difference of mean change in PRO scores from baseline was 1.4 (95% CI, −0.4 to 3.2) at week 12 and 2.5 (95% CI, −0.8 to 5.9) at week 24, favouring ICI combination groups	-

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
	tumours to avoid excessive heterogeneity. **DATA SOURCES** This systematic review and random-effects meta-analysis used RCTs identified in PubMed, MEDLINE, Embase, and Scopus from database inception to June 1, 2021.						**TIME TO DETERIORATION (TTD) IN PROS.** - TTD of PROs was reported in 23 of 34 RCTs (12 RCTs testing ICIs as monotherapy and 4 trials testing ICIs combined with chemotherapy) - TTD was assessed through EORTC QLQ-C30 GHS in 16 trials and EQ-5D-3L VAS in 7 trials. - TTD was longer in the ICI monotherapy group compared with control groups (pooled TTD HR, 0.80; 95% CI, 0.70-0.91) - TTD was longer in the ICIs in combination with chemotherapy groups compared with control groups in all trials (pooled TTD HR, 0.89; 95% CI, 0.78-1.00) **AUTHORS' CONCLUSION** - A favourable association of ICIs with patient quality of life compared with control groups that did not contain immunotherapy, especially when ICIs were administered as monotherapy.	



TRAJECTORIES OVER TIME OF BETWEEN-GROUPS DIFFERENCES IN MEAN CHANGE OF PATIENT-REPORTED OUTCOMES (PROS) ASSESSED IN EACH TRIAL AND POOLED ESTIMATES ACCORDING TO EXPERIMENTAL TREATMENT GROUPS

The difference in mean change of PROs is shown for each treatment comparison (dark blue dashed lines and boxes) and the meta-analytic pooled estimates (solid blue line and boxes) according to experimental treatment groups with corresponding 95% CIs (ie, ICI monotherapy and ICI in combination with chemotherapy). Each dashed line represents a single treatment comparison, and the size of each rectangle reflects the precision of each effect. For trials in which comparisons at 12 and 24 weeks of follow-up were not reported or derivable (orange boxes), these values were estimated using the information at the previous and subsequent available time points. Values below the solid horizontal line favour the control, and values above the line favour immunotherapy.

Evidence Table : **SAFETY (TREATMENT-RELATED ADVERSE EVENTS)**
Question : How safe are Immune Checkpoint Inhibitors treatment options for PD-L1 positive advanced non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
9. Wang Y, Zhou S, Yang F, et al. **Treatment-Related Adverse Events of PD-1 and PD-L1 Inhibitors in Clinical Trials: A Systematic Review and Meta-analysis.** JAMA Oncol. 2019;5(7):1008-1019.	**Systematic review and meta-analysis** **Objective** To investigate the incidences of different treatment-related adverse events associated with PD-1/PD-L1 inhibitors **Study selection** **Inclusion criteria:** (1) cancer therapy clinical trial, (2) participants were treated with a single- agent PD-1 or PD-L1 inhibitor, (3) reported tabulated data on treatment-related adverse events, and (4) published in English. **Data Sources** PubMed, Web of Science, Embase, and Scopus were searched from October 1, 2017, through December 15, 2018. **Main outcome measures** Incidences of treatment-related adverse events and differences between different drugs	I	125 clinical trials involving 20,128 patients	PD-1 and PD-L1 inhibitors - Nivolumab (46 trials) - Pembrolizumab (49 trials) - Atezolizumab (15 trials) - Avelumab (9 trials) - Durvalumab (6 trials)	-	Not mentioned	**OVERALL INCIDENCE OF ADVERSE EVENTS** - Pooled overall mean incidence of all-grade adverse events was 1.66% (95% CI, 1.47%-1.86%) - Pooled mean incidence of grade 3 or higher adverse events was 0.11% (95% CI, 0.08%-0.14%). **Most Common All-Grade Adverse Events** **Pooled incidence (%) (95% CI)** Fatigue 18.26(16.49-20.11) Pruritus 10.61(9.46-11.83) Diarrhea 9.47(8.43-10.58) **Most Common Grade 3 or Higher Adverse Events** **Pooled incidence (%) (95% CI)** Fatigue 0.89 (0.69-1.14) Anaemia 0.78 (0.59-1.02) AST increase 0.75(0.56-0.99) **INCIDENCE OF IMMUNE-RELATED ADVERSE EVENTS** **Most Common All-Grade Adverse Events** **Pooled incidence (%) (95% CI)** **Endocrine dysfunctions** Hypothyroidism 6.07 (5.35-6.85) Hyperthyroidism 2.82 (2.40-3.29) Hyperglycemia 1.20 (0.91-1.55) Thyroiditis 0.75 (0.52-1.04) Adrenal insufficiency 0.69 (0.50-0.93) **Others** Diarrhoea 9.47(8.43-10.58) AST increase 3.39 (2.94-3.89) Vitiligo 3.26 (2.80-3.79) ALT increase 3.14 (2.71-3.62) Pneumonitis 2.79 (2.39-3.23) Colitis 1.24 (0.99-1.54)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							Most Common Grade 3 or Higher Adverse Events **Pooled incidence (%) (95% CI)** **Endocrine dysfunctions** Hyperglycemia 0.24 (0.13-0.38) Adrenal insufficiency 0.18 (0.10-0.30) Type 1 diabetes 0.18 (0.10-0.30) Hypophysitis 0.16 (0.09-0.27) Hypothyroidism 0.08 (0.04-0.13) **Others** AST increase 0.75 (0.56-0.99) ALT increase 0.70 (0.52-0.93) Pneumonitis 0.67 (0.50-0.89) Diarrhoea 0.59 (0.45-0.77) Colitis 0.47 (0.34-0.65) **AUTHORS' CONCLUSION** Different PD-1 and PD-L1 inhibitors may be associated with different incidences of adverse events	

Evidence Table : **SAFETY (SERIOUS ADVERSE EVENTS)**
Question : How safe are Immune Checkpoint Inhibitors treatment options for PD-L1 positive advanced non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
10. Zhou C, Li M, Wang Z, An D, Li B. **Adverse events of immunotherapy in non-small cell lung cancer: A systematic review and network meta-analysis.** Int Immunopharmacol. 2022 Jan;102:108353. doi: 10.1016/j.intimp.2021.108353. Epub 2021 Dec 6. PMID: 34883352.	**Systematic review and meta-analysis** **Objective** To systematically assess the incidences of adverse events (AEs) in immunotherapy of NSCLC RCTs were searched in PubMed/MEDLINE, Embase, Cochrane, and ClinicalTrail.gov before May 2021, and grouped arms into 10 treatment categories. The authors extracted AEs as serious (grade 3–5) or others (grade1-2) from all systems, and pooled their incidences by random effects model. For arm-based pair-wise comparisons, Bayesian network meta-analysis was employed. Meta-regression was used to assess the contribution of coefficients. **Study selection** **Inclusion criteria:** **(i)** Prospective RCTs assessing immunotherapies in NSCLC, which had registered in ClinicalTrials.gov or other clinical trial registries been certified by WHO; **(ii)** The completed results including adverse events have been	I	52 RCTs involving 23,322 patients The majority of included RCTs (27/52) are in phase 3 or phase 4.	According to the treatment intervention, arms were grouped into the following 10 treatment categories: 1. Chemo arm (n = 28) 2. PD1 inhibitors alone (n = 27) 3. PDL1 inhibitors alone (n = 12) 4. CTLA4 alone (n = 2) 5. PD1_Chemo arm (n = 6) 6. PDL1_Chemo arm (n= 5) 7. CTLA4_Chemo arm (n = 1) 8. PD1_CTLA4 arm (n = 4) 9. PDL1_CTLA4 arm (n = 2) 10. ICI_Target therapy (n = 5)	Platinum based-chemotherapy		**SERIOUS AES (GRADE 3–5)** **Pooled overall incidence (95% CI)** Chemo 37.0% (34.0%- 40.0%) PD1 alone 33.0% (27.0%-40.0%) PDL1 alone 37.0% (37.0%-41.0%) CTLA4 alone 52.0% (28.0%-74.0%) PD1- Chemo. 43.0% (33.0%-53.0%) PDL1- Chemo 47.0% (44.0%-50.0%) CTLA4-Chemo 41.0%(32.0%-51.0%) PD1-CTLA4 43.0% (24.0%-64.0%) ICI-Target therapy 48.0% (43.0%-58.0%) **SPECIFIC SERIOUS EVENT** **PNEUMONITIS** **Pooled incidence (95% CI)** PD1 alone 3.24% (2.51%-4.18%) PDL1 alone 2.01% (1.47%-2.75%) Chemo 0.88% (0.66%-1.17%) PD1- Chemo 2.78% (1.35% - 5.62%) PDL1-Chemo 2.78% (2.11% - 3.67%) **COLITIS** **Pooled incidence (95% CI)** PD1 alone 0.8% (0.55%-1.16%) PDL1 alone 0.84% (0.54%-1.29%) Chemo 0.34% (0.21%-0.55%) PD1-Chemo 2.47% (1.47%-4.13%) PDL1-Chemo 0.85% (0.51%-1.44%) **HEPATOBILIARY DISORDERS** **Pooled incidence (95% CI)** PD1 alone Hepatitis 0.9% (0.61%-1.34%) ALT increased 0.74%(0.47%-1.16%) AST increased 0.83%(0.53%-1.29%) PD-L1 alone Hepatitis 1.01%(0.29%-3.47%)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
	published in ClinicalTrail.gov or peer-reviewed journal articles; **(iii)** English-language publications. **Exclusion criteria:** **(i)** Retrospective trials or analyses; (ii) No 30 people in each arm; (iii) Trials unlimited cancer types and couldn't be extracted the results of NSCLC						ALT increased 0.51%(0.27%-0.98%) AST increased 0.51%(0.27%-0.98%) <u>Chemo</u> Hepatitis 0.25% (0.14%-0.46%) ALT increased 0.31%.(0.19%-0.52%) AST increased 0.23% (0.13%-0.42%) <u>PD1+chemo</u> Hepatitis 1.51%(0.67%-3.37%) ALT increased 0.73%[0.24%-2.25%) AST increased 0.84%(0.29%-2.37%) <u>PDL1+chemo</u> Hepatitis 0.57% (0.3%-1.09%) ALT increased 0.39% (0.14%-1.1%) AST increased 0.28% (0.1%-0.74%) **MYOCARDITIS** **Pooled incidence (95% CI)** PD1 0.34% (0.08%-1.51%) PDL1 0.49% (0.17%-1.4%) Chemo 0.25% [0.09%-0.71%) **RASH** **Pooled incidence (95% CI)** PD1 alone 0.6% (0.28%-1.27%) PDL1 alone 0.5% (0.27%-0.93%) Chemo 0.24% (0.14%-0.4%) PD1 + Chemo 1.85% (0.67%-4.99%) PDL1 + Chemo 0.68% (0.37%-1.23%) PDL1+ CTLA4 0.28% (0.06%-1.35%) **AUTHORS' CONCLUSION** - The overall incidences of serious AEs were no lower in immunotherapy arms than chemotherapy arms. - The incidences of each kind of serious AEs were less than 4% in monotherapy, and slightly higher in combined groups. - -The immune related AEs of serious pneumonitis, colitis, hepatitis, and rash presented a significant higher incidence rank in the immunotherapy groups compared to chemotherapy.	

Evidence Table : **SAFETY**
Question : How safe are Immune Checkpoint Inhibitors treatment options for PD-L1 positive advanced non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
11. Chen CY, Huang CH, Chen WC, et al. **Comparative safety of immune checkpoint inhibitors and chemotherapy in advanced non-small cell lung cancer: A systematic review and network meta-analysis.** Int Immunopharmacol .2022;108:108848.	**Systematic review and network meta-analysis** **Objective** To provide a toxicity profile and safety ranking of different ICI and CT combination regimens. **Study selection** **Inclusion criteria:** **(i)** Those that enrolled patients with treatment-naïve advanced (stage IIIB/IIIC/IV) NSCLC; **(ii)** randomized clinical trials (RCTs) using ICI monotherapy or in combination with other ICIs or CT; and **(iii)** phase 2 and 3 trials reporting grade 3–5 or any grade of TRAEs or irAEs according to the definitions and criteria of the recruited clinical trials. **Searches** PubMed, Embase, Cochrane Library, and CENTRAL databases for relevant studies published up to July 1, 2021. Abstracts or presentations of international scientific conferences including the American Society of Clinical Oncology (ASCO), American Association for Cancer Research (AACR), European Society for Medical Oncology (ESMO), and World Conference on Lung Cancer (WCLC) were also checked to ensure that the most recent updated data were included.	I	21 RCTs involving 12,626 patients, conducted between 2016 and 2021 - 20 phase III RCTs - 1 phase II RCTs - 16 trials were open labelled trials *KEYNOTE 021* *KEYNOTE 024* *KEYNOTE 042* *KEYNOTE 189* *KEYNOTE 407* *KEYNOTE 598* *CheckMate 026* *CheckMate 227* *CheckMate 9LA* *IMpower 130* *IMpower 131* *IMpower 132* *MYSTIC* *CCTG BR-34* *CAMEL* *ORIENT-11* *ORIENT-12* *RATIONAL 304* *RATIONAL 307*	**4 different treatment regimens** - ICI-CT - ICI-ICI-CT - ICI-ICI - ICI monotherapy - Pembrolizumab (5 trials) - Nivolumab (3 trials) - Atezolizumab (4 trials) - Durvalumab (2 trials) - Tislelizumab (2 trials) - Sintilimab (2 trials) - Cemiplimab (1 trial) - Camrelizumab (1 trial) - Pembrolizumab plus nivolumab (1 trial)	Standard chemotherapy	Median follow-up 8-59.9 months	**RISK TREATMENT-RELATED ADVERSE EVENTS (TRAEs)** **Risk of any grade TRAEs** **Pooled ORs (95%CrI)** *(in comparison to CT)* ICI-CT 1.99 (1.34, 2.99) ICI-ICI-CT 1.27 (0.67, 2.44) ICI-ICI 0.52 (0.35, 0.77) ICI monotherapy 0.28 (0.21, 0.38) - Compared to CT alone, a significantly higher risk of any TRAEs was observed with ICI-CT - Risk of any TRAEs was comparable between ICI and ICI-CT combinations and CT alone - A lower risk of TRAEs was found with ICI **Risk of grade 3-5 TRAE** **Pooled ORs (95%CrI)** *(in comparison to CT)* ICI-CT 1.60 (1.36, 1.89) ICI-ICI-CT 1.26 (0.81, 1.89) ICI-ICI 0.68 (0.53, 0.87) ICI monotherapy 0.35 (0.29, 0.42) - A higher risk of grade 3–5 TRAEs was demonstrated with ICI-CT combi- nations compared to CT alone - A lower risk of grade 3–5 TRAEs was demonstrate with ICI and ICI-ICI combinations compared to CT alone **Ranking profile on TRAE** - The ranking profiles for different regimens on the risk of any grade and	**ICI** = immune checkpoint inhibitor **CT** = chemotherapy

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments

All grade TRAE	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
ICI-CT	0.883	0.117	0	0	0
ICI-ICI-CT	0.116	0.662	0.215	0.006	0
CT	0	0.221	0.777	0.002	0
ICI-ICI	0	0	0.008	0.989	0.003
ICI	0	0	0	0.00	0.997

Grade3-5 TRAE	Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
ICI-CT	0.871	0.129	0	0	0
ICI-ICI-CT	0.129	0.739	0.126	0.007	0
CT	0	0.132	0.867	0.002	0
ICI-ICI	0	0	0.008	0.992	0
ICI	0	0	0	0	1.000

All grade irAEs	Rank 1	Rank 2	Rank 3	Rank 4
ICI_ICI	0.976	0.023	0.001	0
ICI	0.024	0.972	0.004	0
ICI_CT	0	0.005	0.995	0
CT	0	0	0	1.000

Grade 3-5 irAEs	Rank 1	Rank 2	Rank 3	Rank 4
ICI_ICI	0.998	0.002	0	0
ICI	0.002	0.998	0	0
ICI_CT	0	0	0.999	0
CT	0	0	0	1.000

grade 3–5 TRAEs were the same, showed that ICI-CT combinations were associated with the greatest risk (probability: 88.3% and 87.1%), followed by ICI-ICI-CT (66.2% and 73.9%), CT alone (77.7% and 86.6%), ICI-ICI (98.9% and 99.2%), and ICI monotherapy (99.7% and 100%), respectively

RISK IMMUNE-RELATED ADVERSE EVENTS (IrAEs)

Risk of any grade IrAEs

	Pooled ORs (95%CrI) *(in comparison to CT)*
ICI-ICI	12.6 (5.83, 27.60)
ICI monotherapy	6.42 (3.79, 11.30)
ICI -CT	2.49 (1.71, 3.74)

- A significantly higher risk of any irAEs was found with ICI monotherapy and ICI-ICI compared to CT alone

Risk of grade 3-5 IrAE

	Pooled ORs (95%CrI) *(in comparison to CT)*
ICI-ICI	22.0 (10.4, 54.7)
ICI monotherapy	7.59 (4.16, 16.3)
ICI-CT	2.19 (1.58, 3.03)

- The risk of grade 3–5 irAEs was consistent to that of all grade irAEs,

Ranking profile on IrAEs

- The ranking profiles for different regimens on the risk of any grade and grade 3–5 irAEs were the same.
- The ranking order of ICI-ICI (probability: 97.6% and 99.8%), ICI monotherapy (97.2% and 99.8%), ICI-CT (99.5% and 99.9%), and CT alone (99.9% and 100%), respectively

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							- The incidence of any grade and grade 3–5 irAEs was lower when adding CT to ICI monotherapy. **System or organ-specific irAEs** - ICI-ICI-CT was associated with the highest risk of irAEs in endocrine, hepatic, dermatologic irAEs, and infusion reactions - ICI-ICI was associated with the greatest risk of irAEs in gastrointestinal, hepatic irAEs and pneumonitis. - ICI-CT was associated with the highest risk of renal irAEs. **AUTHORS' CONCLUSION** - This NMA demonstrated that ICI-CT combinations were associated with a higher incidence of any grade or grade 3–5 TRAEs compared to ICI-ICI combinations or ICI monotherapy. - ICI-ICI-CT combinations were not associated with a higher incidence of any grade or grade 3–5 TRAEs than ICI-CT combinations. - The incidence of any grade and grade 3–5 irAEs was lower when CT was added to ICI monotherapy. - System or organ specific irAEs demonstrated that the incidence of irAEs ranked from high to low for ICI-ICI, ICI monotherapy, ICI-CT, and CT alone in terms of endocrine, hepatic, dermatologic, and respiratory-related irAEs.	

Evidence Table : **SAFETY (IMMUNE-RELATED ADVERSE EVENTS)**
Question : How safe are Immune Checkpoint Inhibitors treatment options for PD-L1 positive advanced non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
12. Zhang W, Gu J, Bian C, Huang G. **Immune-Related Adverse Events Associated With Immune Checkpoint Inhibitors for Advanced Non-small Cell Lung Cancer: A Network Meta-Analysis of Randomized Clinical Trials.** Front Pharmacol. 2021 Oct	**Systematic review and network meta-analysis** **Objective** To compare the probability of immune related AEs caused by ICI + platinum, ICI alone, dual ICIs combination for advanced NSCLC through NMA. RCTs on ICIs versus platinum-based chemotherapy as the first-line treatment of advanced NSCLC from 2015 to 2020 were searched in PubMed, Embase. The surface under the cumulative ranking curve (SUCRA) metric was a tool to rank the probabilities of irAEs of each treatment and identify the best treatment. The SUCRA value was ranged from 0 to 1, the closer to 1 this value approached, the higher its incidence of an immune-related adverse event was in this network meta-analysis. **Study selection** **Inclusion criteria:** **(i)** Study type: only Phase II or III double blind RCTs for advanced NSCLC; **(ii)** participants: included patients that were pathologically diagnosed as advanced NSCLC; (iii) experimental group: patients were treated with immunotherapy alone or an immune-based combination as first-line	I	12 head-to-head phase II and III RCTs involving 8,453 patients with advanced NSCLC *Checkmate 026* *Mystic* *Keynote-407* *Keynote-189* *Keynote-042* *Keynote-024* *Keynote-021* *IMpower 132* *IMpower 131* *IMpower 130* *IMpower 110* *Checkmate 227* Phase III trials – 9 studies **Study sites**: Multinational – 9 studies US – 2 studies Taiwan – 1 study **Sample size**: 123- 1274	**8 treatment regimes** 1. Pembrolizumab 2. Nivolumab 3. Durvalumab 4. Atezolizumab 5. Pembrolizumab + platinum 6. Atezolizumab + platinum 7. Nivolumab + ipilimumab 8. Platinum-based chemotherapy).	Platinum based chemotherapy	-	**IMMUNE RELATED ADVERSE EVENTS** **1. Dermatologic irAEs (pruritus and rash)** (11 studies; 7 treatment regimens) **SUCRA RANKING** **Pooled RR (95% CI)** *(in comparison to platinum-based chemotherapy)* NIV + IPI 6.20 (3.23–11.88) PEM 3.80 (2.03–7.1) NIV 2.91 (1.74–4.86) PEM + CT 1.95 (1.24–3.06) ATE + CT 1.85 (1.21–2.82) DURVA 1.23 (0.62–2.42) **2. Endocrine irAEs (hypothyroidism and hyperthyroidism)** (11 studies; 7 treatment regimens) **SUCRA RANKING** **Pooled RR (95% CI)** *(in comparison to platinum-based chemotherapy)* NIV + IPI 14.43 (1.89–110.2) DURVA 10.58 (2.03–55.18) PEM 8.26 (2.85–23.97) ATE + CT 7.93 (2.78–22.63) NIV 5.77 (1.28–25.98) PEM + CT 4.22 (1.76–10.14) **3. Colitis** (10 studies; 6 treatment regimens) **SUCRA RANKING** **Pooled RR (95% CI)** *(in comparison to platinum-based chemotherapy)* ATE + CT 8.59 (1.61–45.85) NIV 6.97 (0.36–135.67) PEM 4.65 (1.17–18.54) DURVA 2.87 (0.12–70.68) PEM+CT 2.59 (0.89–7.51) **4. Pneumonitis** (11 studies; 7 treatment regimens) **SUCRA RANKING** **Pooled RR (95% CI)** *(in comparison to platinum-based chemotherapy)* PEM 22.06 (3.71–131.10)	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
	treatment, control group: patients were treated with only platinum-based chemotherapy as first-line treatment; **(iv)** outcome indicators: there was at least one irAE in the RCT **Exclusion criteria:** non-English articles, studies without valid data, reviews, meta-analyses, editorials, commentary letters, repeat studies.						PEM+CT 3.62 (0.76–17.24) DURVA 3.48 (0.60–20.28) ATE + CT 2.84 (0.66–12.26) NIV 1.83 (0.33–10.28) ATE 1.34 (0.39–4.65) **5. Hepatitis** (10 studies; 6 treatment regimens) **SUCRA RANKING** **Pooled RR (95% CI)** *(in comparison to platinum-based chemotherapy)* PEM 8.26 (0.98, 69.47) PEM+CT 6.10 (1.08–34.41) DURVA 4.80 (0.23–100.25) ATE+CT 4.13 (0.89–19.15) NIV 2.97 (0.12–73.14) **AUTHORS' CONCLUSION** ICI-based therapy showed a higher incidence of irAEs than platinum-based chemotherapy	

Evidence Table : **SAFETY (TREATMENT-RELATED DEATH)**
Question : How safe are Immune Checkpoint Inhibitors treatment options for PD-L1 positive advanced non-small cell lung cancer patients ?

<table>
<tr><th>Bibliographic Citation</th><th>Study Type/ Methods</th><th>LE</th><th>Number of Patients & Patient Characteristic</th><th>Intervention</th><th>Comparison</th><th>Length of Follow Up (If Applicable)</th><th>Outcome Measures/ Effect Size</th><th>General Comments</th></tr>
<tr>
<td>13. Yu X, Zhang X, Yao T, et al. Fatal Adverse Events Associated With Immune Checkpoint Inhibitors in Non-small Cell Lung Cancer: A Systematic Review and Meta-Analysis. Front Med (Lausanne). 2021;8:627089.</td>
<td>Systematic review and meta-analysis

Objective
To evaluate the risk of fatal adverse events (FAEs) in NSCLC patients administered with ICIs.

Study selection
Inclusion criteria:
[i] participants: patients histologically diagnosed as NSCLC; [ii] intervention: ICI monotherapy alone or combined with immunotherapy, chemotherapy, target therapy, and radiotherapy; [iii] comparison: the independent control arm administered with chemotherapy; [iv] outcomes: reporting the treatment-related FAEs; [v] randomized controlled trials (RCTs).

Exclusion criteria:
[i] reviews and quality of life studies, [ii] animal studies or basic experiments, [iii] single arm trials, and [iv] non-English articles.

Searches
PubMed, EMBASE, Cochrane library database from inception to September 16, 2020. Conference abstracts from annual meetings of the American Society of Clinical Oncology and European Society for Medical Oncology in the years 2010–2020 were also searched.</td>
<td>I</td>
<td>20 RCTs involving 13,483 patients
- 18 phase III RCTs
- 4 phase II RCTs

KEYNOTE-042
KEYNOTE-024
KEYNOTE-010
KEYNOTE-407
KEYNOTE-021
CheckMate 078
CheckMate 227
CheckMate 026
CheckMate 057
CheckMate 017
ARCTIC
MYSTIC
JAVELIN Lung 200
OAK
POPLAR
IMpower131
IMpower130
IMpower150
CA184-104
CA184-041
MYSTIC</td>
<td>1. Anti PD-1 monotherapy (7 trials)
2. Anti PD-1 combination with chemotherapy (4 trials)
3. Anti-PD-L1 monotherapy (5 trials)
4. Anti PD-L1 combination with chemotherapy (3 trials)
5. Anti-CTL4 combine with chemotherapy (2 trials)</td>
<td>Standard chemotherapy</td>
<td>Not mentioned</td>
<td>OVERALL INCIDENCE OF TREATMENT-RELATED FATAL ADVERSE EVENTS

Pooled Incidence % (95%CI)

ICI 0.65 (0.31- 1.07)
Dual ICI 1.47 (0.78-2.36)
ICI-chemotherapy 2.01 (1.42-2.69)
Chemotherapy 1.17 (0.74-1.69)

The overall incidence of FAEs among all patients in the reviewed studies was 1.12% (95% CI = 0.83–1.45, I2 = 57.40%).

INCIDENCE AND RISK OF SYSTEM-SPECIFIC FAE IN ICI AND CHEMOTHERAPY
<table>
<tr><th></th><th>System</th><th colspan="2">ICI</th><th colspan="2">Chemotherapy</th><th>RR</th><th>95% CI</th><th>P-value</th></tr>
<tr><th></th><th></th><th>Events/total</th><th>%</th><th>Events/total</th><th>%</th><th></th><th></th><th></th></tr>
<tr><td>Monotherapy</td><td>Infections and infestations</td><td>6/3,774</td><td>0.16</td><td>24/3,283</td><td>0.73</td><td>0.29</td><td>0.13-0.63</td><td>0.002</td></tr>
<tr><td></td><td>Respiratory system disorders</td><td>18/3,681</td><td>0.49</td><td>12/3,034</td><td>0.40</td><td>1.17</td><td>0.59–2.34</td><td>0.656</td></tr>
<tr><td></td><td>Blood and lymphatic system disorders</td><td>0/3,025</td><td>0</td><td>10/2,559</td><td>0.39</td><td>0.23</td><td>0.07–0.73</td><td>0.013</td></tr>
<tr><td></td><td>Cardiac disorders</td><td>5/2,190</td><td>0.23</td><td>4/1,580</td><td>0.25</td><td>0.89</td><td>0.29–2.72</td><td>0.834</td></tr>
<tr><td></td><td>Metabolism and nutrition disorders</td><td>0/1,711</td><td>0</td><td>3/1,289</td><td>0.23</td><td>0.25</td><td>0.04–1.54</td><td>0.136</td></tr>
<tr><td></td><td>Renal and urinary disorders</td><td>1/393</td><td>0.25</td><td>1/365</td><td>0.27</td><td>0.93</td><td>0.06–14.79</td><td>0.958</td></tr>
<tr><td></td><td>Nervous system disorders</td><td>2/1,314</td><td>0.15</td><td>1/1,270</td><td>0.08</td><td>1.35</td><td>0.26–6.89</td><td>0.718</td></tr>
<tr><td></td><td>Vascular disorders</td><td>1/973</td><td>0.10</td><td>1/771</td><td>0.13</td><td>0.70</td><td>0.12–4.10</td><td>0.693</td></tr>
<tr><td></td><td>Gastrointestinal disorders</td><td>1/636</td><td>0.16</td><td>0/615</td><td>0</td><td>2.90</td><td>0.12–71.08</td><td>0.514</td></tr>
<tr><td></td><td>Hepatobiliary</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td></tr>
<tr><td></td><td>Death not otherwise specified</td><td>3/1,325</td><td>0.23</td><td>3/1,265</td><td>0.24</td><td>0.96</td><td>0.26–3.51</td><td>0.947</td></tr>
<tr><td>Combination</td><td>Infections and infestations</td><td>9/1,709</td><td>0.53</td><td>10/1,485</td><td>0.67</td><td>0.86</td><td>0.37–2.02</td><td>0.734</td></tr>
<tr><td></td><td>Respiratory system disorders</td><td>12/1,316</td><td>0.91</td><td>5/1,089</td><td>0.46</td><td>1.99</td><td>0.75–5.26</td><td>0.165</td></tr>
<tr><td></td><td>Gastrointestinal disorders</td><td>1/393</td><td>0.25</td><td>2/394</td><td>0.51</td><td>0.50</td><td>0.05–5.51</td><td>0.572</td></tr>
<tr><td></td><td>Nervous system disorders</td><td>1/393</td><td>0.25</td><td>1/394</td><td>0.25</td><td>1.00</td><td>0.06–15.97</td><td>0.999</td></tr>
<tr><td></td><td>Renal and urinary disorders</td><td>0/278</td><td>0.00</td><td>1/280</td><td>0.36</td><td>0.34</td><td>0.01–8.21</td><td>0.503</td></tr>
<tr><td></td><td>Cardiac disorders</td><td>5/1,085</td><td>0.46</td><td>1/846</td><td>0.12</td><td>1.99</td><td>0.44–9.09</td><td>0.374</td></tr>
<tr><td></td><td>Blood and lymphatic system disorders</td><td>4/624</td><td>0.64</td><td>1/639</td><td>0.16</td><td>2.27</td><td>0.51–10.17</td><td>0.283</td></tr>
<tr><td></td><td>Hepatobiliary</td><td>3/1,085</td><td>0.28</td><td>0/846</td><td>0.00</td><td>2.39</td><td>0.39–14.79</td><td>0.348</td></tr>
<tr><td></td><td>Vascular disorders</td><td>2/565</td><td>0.35</td><td>0/577</td><td>0.00</td><td>3.10</td><td>0.32–29.67</td><td>0.327</td></tr>
<tr><td></td><td>Metabolism and nutrition disorders</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td><td>–</td></tr>
<tr><td></td><td>Death not otherwise specified</td><td>3/751</td><td>0.40</td><td>0/512</td><td>0.00</td><td>2.99</td><td>0.36-24.78</td><td>0.309</td></tr>
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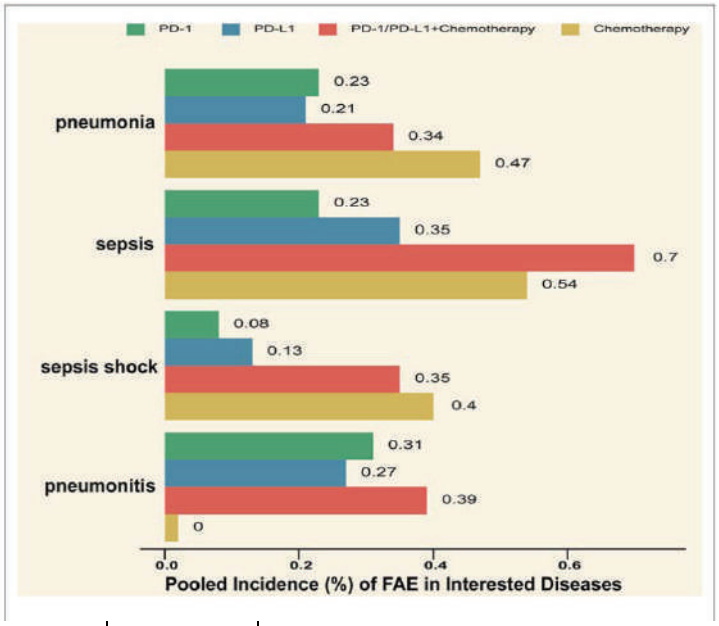
Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
							- ICI monotherapy was associated with lower incidence of FAEs caused by blood system disorders (RR = 0.23, 95% CI = 0.07–0.73, p = 0.013, I^2 = 0%) and infectious diseases (RR = 0.29, 95% CI = 0.13–0.63, p = 0.002, I^2 = 0%). - No statistical differences were found in other systems. - Comparison between combination therapy and chemotherapy showed that, in the former, the percentage of almost all FAEs was higher than in the latter, although this difference did not reach statistical significance. This finding suggests a potential risk of combined therapy.  - For infectious diseases, the pooled incidence of FAEs among the patients who received chemotherapy was remarkably higher than among those who received ICI monotherapy - The incidence of pneumonitis, which was a major cause of death among the patients	

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							who received ICI monotherapy (10/38) and was related to a potential immunologic cause. The incidence of fatal pneumonitis in ICI therapy was ~0.3%. - In comparison to chemotherapy, the application of ICI was significantly related to an increase in the incidence of pneumonitis (RR = 5.72, 95% CI = 1.14–28.80, p= 0.03, I^2 = 0%). **AUTHORS' CONCLUSION** - Overall, compared to conventional chemotherapy, ICI monotherapy was found to decrease the risk of FAEs, while the combined therapy (with another ICI or chemotherapy) had the opposite tendency. - While the patients who received chemotherapy mainly suffered from the risks of death from myelosuppression and infection, those who received immunotherapy were mainly threatened by immune-related pneumonitis.	

Evidence Table : **COST-EFFECTIVENESS**
Question : How cost-effective are Immune Checkpoint Inhibitors treatment options for PD-L1 positive advanced non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
14. Li N, Zheng H, Zheng B, Chen C, Cai H, Liu M. **Economic Evaluations of Immune Checkpoint Inhibitors for Patients with Non-Small Cell Lung Cancer: A Systematic Review.** Cancer Manag Res. 2020 Jun 12;12:4503-4518..	**Systematic review** **Objective** To assess the quality of available evidence on the economic evaluations of immune checkpoint inhibitors in patients with non-small cell lung cancer (NSCLC) and provide evidence to improve the efficiency of healthcare resources. Literature search was performed using some electronic databases (PubMed, Embase and Cochrane Central Register of Controlled Trials). Final search was performed in December 2019. Study characteristics and results were recorded and compared. The quality of the studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklists. **Study selection** **Inclusion criteria** (i) full economic evaluations (cost-minimization, cost–benefit, cost-effectiveness, and cost–utility analyses) of immune checkpoint inhibitors for patients with NSCLC (ii) immunotherapies compared with chemotherapy or with	I	21 studies included Publication between 2016 and 2019. **Country of origin** - US -12 studies - UK – 2 studies - France – 1 study - Canada – 2 studies - Australia – 1 study - Switzerland – 1 study - China – 3 studies - Hong Kong – 1 study **Type of analysis** Cost-effectiveness analysis with reported outcome in terms of **cost per quality-adjusted life years (QALYs)** and **cost per life year (LY) gained**. **Type of treatment** - First line treatment (16 studies) - Second line treatment (5 studies) **PD-L1 status** - PD-L1 positive or high (14 studies) - The other studies were not clearly stated. **The included studies were mainly based on the following clinical trials:** KEYNOTE 024 KEYNOTE 042 KEYNOTE 189 KEYNOTE 407 KEYNOTE 010	- Pembrolizumab (14 studies; 13 studies as 1st line) - Nivolumab (4 studies) - Atezolizumab (3 studies)	Platinum based-chemotherapy or docetaxel		**PEMBROLIZUMAB** **Pembrolizumab vs platinum-based chemotherapy** United State **WTP** : $100,000 (US payer perspective) - $194,000/QALY (US third-party public healthcare payers) 1. PD-L1>50% **ICER** : $36,493/QALY - $136,228.82/QALY $76,390.48/LY - $91,063/LY 2. PD-L1 1-49% **ICER**: $39,404/QALY - 179,530.17/QALY $134,227/LY - $101,763.74/LY UK **Perspective:** UK health care perspective **WTP**: £50,000/QALY **ICER**: £86,913/QALY France **Perspective** : Healthcare system perspective **WTP**: No statement **ICER**: €78,729/ QALY, €62,846/LY Pembrolizumab appears cost-effective versus chemotherapy for first-line treatment of PD-L1-positive (50%) metastatic NSCLC patients. China **Perspective**: Chinese payer perspective **WTP**:: $26,508/QALY **ICER**: PD-L1≥50% patients $36,493/QALY PD-L1≥20% patients $42,311/QALY PD-L1≥1% patients $39,404/QALY	**QALY** = quality adjusted life year **LY** = life years

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	each other and those used as first- or second-line treatment, (iii) the incremental analysis method was used to decide whether the higher cost of the therapeutic regimen relative to the lower plan can bring a satisfactory incremental income, and (iv)) use of English language in reporting. **Exclusion criteria** Articles that focused on diagnostics and adherence, partial economic evaluations, and conference abstract.		CheckMate 057 CheckMate 017 CheckMate 078 OAK trial IMpower150 **Time horizon** - 6 years (1 study) - 10 years (4 studies) - 20 years (7 studies) - Lifetime (6 studies) - No statement (3 studies) **Discount rate** 3% (16 studies) 3.5% (1 study) 2% (1 study) **Model based** - Markov model (9 studies) - Partitioned survival model (8 studies) - Markov model + partitioned- survival model (2 studies) - Combining a decision tree and the Markov model (1 study) - Microsimulation model (2 studies) **Perspective of Analysis** - Health- care system perspective (n = 9) - Third-party healthcare payer (n = 9) - Publicly funded healthcare system (n = 2) - Social perspective (n = 1) **Health state** 3 key health statuses: progression free,				**Pembrolizumab + chemotherapy vs chemotherapy** United State **WTP**: $100,000- $540,000/QALY **ICER**: $86,293 - $194,372/QALY and $87,242/LY PD-L1≥50% patients $99,777 - $103,402/QALY, PD-L1 1–49% patients $66,837 - $85,986/QALY, PD-L1<1% patients $87,507- $183,529/QALY. **Pembrolizumab vs platinum doublet chemotherapy** UK **Perspective**: British National Health System (NHS) **WTP**: $42,000/ QALY **ICER**: $43,000 – $69,000/QALY Hong Kong **Perspective:** The Hospital Authority in Hong Kong **WTP:** $130,490/QALY **ICER:** $110,922/QALY, $89,419/ LY **Pembrolizumab versus docetaxel** US **Perspective**: US third-party payer healthcare **WTP**: No statement (3-times GDP per capita) **ICER**: $168,619/QALY **ATEZOLIZUMAB** **Atezolizumab vs docetaxel** Canada **Perspective**: The Canadian publicly-funded health care system **WTP**: No statement **ICER**: $142,074/ QALY, $103,726/LY atezolizumab dominates nivolumab Atezolizumab represents a cost-effective therapeutic option for the treatment of patients with advanced NSCLC who progress after first-line platinum doublet chemotherapy.	

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
			progressed disease, and death.				**NIVOLUMAB** **Nivolumab vs docetaxel** <u>Canada</u> **Perspective**: A publicly funded healthcare system **WTP**: No statement **ICER**: $152,229/QALY Nivolumab was found to involve a trade- off between improved patient survival and QALYs, and increased cost. <u>AUstralia</u> **Perspective**: Australian healthcare system perspective **WTP**: A$50,000/QALY **ICER**: A$220,029/ QALY, A$193,459/LY <u>Switzerland</u> **Perspective**: Swiss healthcare system perspective **WTP**: CHF100, 000/ QALY **ICER**: CHF177,478/QALY **PD-L1 positive**: CHF124,891/ QALY <u>China</u> **Perspective**: The Chinese healthcare system **WTP**: $28,899/QALY **ICER**: $93,307/QALY, $74,126/LY **AUTHORS' CONCLUSION** The included studies indicated that pembrolizumab regimens are cost-effective as first-line treatment for patients with NSCLC in developed countries. Nivolumab and atezolizumab are likely to be cost-effective as second-line treatment but not as first-line treatment.	

Evidence Table : **COST-EFFECTIVENESS**
Question : How cost-effective are Immune Checkpoint Inhibitors treatment options for PD-L1 positive advanced non-small cell lung cancer patients ?

Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
15. Barbier MC, Pardo E, Panje CM, Gautschi O, Lupatsch JE; Swiss Group for Clinical Cancer Research (SAKK). **A cost-effectiveness analysis of pembrolizumab with or without chemotherapy for the treatment of patients with metastatic, non-squamous non-small cell lung cancer and high PD-L1 expression in Switzerland**. Eur J Health Econ. 2021 Jul;22(5):669-677.	**Economic evaluation study** **Objective** To conduct a cost-effectiveness analysis for Switzerland comparing Pembrolizumab monotherapy or in combination with chemotherapy for patients with metastatic non-squamous non-small cell lung cancer (NSCLC) and high (≥ 50%) programmed death ligand 1 (PD-L1) expression. **Method:** A 3-state Markov model with a time horizon of 10 years was constructed. Parametric functions were fitted to Kaplan–Meier overall survival (OS) and progression-free survival (PFS) using 2-year follow-up data from the KN-024 and KN-189 registration trials. Estimated costs for further treatment lines and costs for best supportive care were included. Costs were assessed from the Swiss healthcare payer perspective. Published utility values were used. Incremental cost-effectiveness ratio (ICER) of the pembrolizumab combination strategy versus pembrolizumab monotherapy and of		- A patient population with the characteristics of the KN-024 and KN-189 registration trials comprising of adult patients with **previously untreated stage IV**, mainly non-squamous NSCLC (100% non-squamous in KN-189, 81.6% in KN-024), **without EGFR or ALK alterations**. -In KN-024, only patients with PD-L1 expression ≥ 50% had been recruited. Since in KN-189, PD-L1 expression was not limited, we only used the subpopulation of patients with PD-L1 expression ≥ 50%.	**3 treatment strategies** 1. Combination strategy (first line pembrolizumab plus chemotherapy, followed by second line treatment with chemotherapy and best supportive care (BSC) or BSC directly) 2. Pembrolizumab strategy (first line pembrolizumab, followed by second line chemotherapy and BSC or BSC directly) 3. Chemotherapy strategy (first line chemotherapy, followed by second line pembrolizumab and BSC or BSC directly) Patients receiving second line treatment were simulated to receive Docetaxel (after first combination) for 4 cycles (= 2.76 months), platinum-based chemotherapy (carboplatin + paclitaxel, carboplatin + pemetrexed) for 4 cycles (after first pembrolizumab), followed by pemetrexed maintenance therapy for up to 35 cycles or until disease progression (only for patients on second line pemetrexed), or second line pembrolizumab until progression (after first line chemotherapy).	Platinum based chemotherapy	2 years	**Pembrolizumab combination strategy versus Pembrolizumab strategy** - Combination therapy resulted in an expected gain of 0.17 quality-adjusted life years (QALYs) per patient and incremental costs of Swiss Francs (CHF) 81,085 as compared to pembrolizumab. These estimates led to an ICER) of CHF **475,299/QALY**. **Pembrolizumab strategy versus chemotherapy strategy** - Pembrolizumab in comparison to chemotherapy was estimated to generate mean incremental QALYs of 0.83 and incremental costs of CHF 56,585, resulting in an ICER of CHF **68,580/QALY**. **SENSITIVITY ANALYSIS** - Results were most sensitive to changes in costs of first line pembrolizumab and combination therapy, together with changes in PFS. - In the probabilistic sensitivity analysis, the authors estimated combination therapy was cost-effective in 4.9% of the simulations and pembrolizumab monotherapy in 82.9%, assuming a willingness-to-pay threshold of CHF 100,000 per QALY gained. **AUTHORS' CONCLUSION** Pembrolizumab is likely to be cost-effective from the Swiss healthcare payer perspective, whereas pembrolizumab plus chemotherapy is not.	

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	pembrolizumab monotherapy versus chemotherapy were assessed in Switzerland, expressed as costs [in Swiss Franc (CHF)] per QALY gained. **Perspective**: Swiss healthcare payer **WTP**: CHF 100,000 per QALY gained. **Time horizon** : 5 years **Discount rates**: 0% and 5% **Adverse events** The model considered the occurrence of all reported grade 3 to 4 adverse events (AEs) from KN-024 and KN-189. The authors separated pneumonitis, anaemia, colitis, exanthema (KN-024) and rash (KN-189), and summarized the remaining AEs in a category "other grade 3–4 toxicities". **Utility** Published utilities (QALYs) for PFS under first treatment as provided by Huang et al., and utility values as reported by the National Institute for Health and Care Excellence (NICE) health in its technology assessment (HTA) report for progression-free disease, stratified by second treatment							

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	Costs Costs included regimen costs (drug costs), application costs (e.g. intravenous administration), diagnostic costs (e.g. computer tomography (CT) scans), costs for AEs of 1L treatment, and costs for other consumables and clinical visits.							

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Bibliographic Citation	Study Type/ Methods	LE	Number of Patients & Patient Characteristic	Intervention	Comparison	Length of Follow Up (If Applicable)	Outcome Measures/ Effect Size	General Comments
16. Peng Y, Zeng X, Peng L, Liu Q, Yi L, Luo X, Li S, Wang L, Qin S, Wan X, Tan C. **First-Line Atezolizumab for Metastatic NSCLC with High PD-L1 Expression: A United States-Based Cost-Effectiveness Analysis.** Adv Ther. 2021 May;38(5):2447-2457.	**Economic evaluation study** **Objective** To evaluate the cost-effectiveness of atezolizumab as the first-line treatment for NSCLC with high programmed cell death ligand 1 (PD-L1) expression from the US payer perspective. **Methods**: A Markov model with three health states was developed to estimate the lifetime cost and outcome of atezolizumab versus platinum- based chemotherapy in patients with previously untreated NSCLC with high PD-L1 expression. High expression of PD-L1 was defined as PD-L1 expression on C 50% of tumour cells or C 10% of tumour-infiltrating immune cells. **3 health states** - Progression-free disease - Progressed disease - Death **Time horizon**: Lifetime **Discount rate** : 3% per year **WTP**: US$100,000 and $150,000 per QALY **Perspective** : US payer **Clinical Data Inputs** IMpower110 trial		Patients with previously **untreated** NSCLC with high PD-L1 expression IMpower110 trial	2 first-line interventions: (1) atezolizumab, and (2) platinum-based chemotherapy for 6 doses. After disease progression, both groups could receive second-line treatment until death. Atezolizumab administered at a dose of 1200 mg every 3 weeks	Platinum-based chemotherapy arm Pemetrexed (500 mg/m2) and cisplatin (75 mg/m2) were given to patients with non-squamous NSCLC; and gemcitabine (1250 mg/m2) and cisplatin (75 mg/m2) were given to patients with squamous NSCLC.	-	The base-case results showed that the life expectancy of patients receiving atezolizumab was 3.75 LYs, which was 2.08 LYs longer than those receiving platinum-based chemotherapy. Atezolizumab produced an additional 1.32 quality-adjusted life-years (QALYs) (2.08 LYs) compared with platinum-based chemotherapy, with incremental **US$170,730 per QALY** ($108,205 per life-year) gained. Atezolizumab was estimated not to be cost-effective compared with platinum- based chemotherapy in the first-line setting treatment of patients with NSCLC with high PD-L1 expression at the willing- to-pay threshold of $100,000/QALY to $150,000/QALY from the US payer perspective. The probability of Atezolizumab being cost-effective compared with platinum-based chemotherapy was 10.28% and 37.71% when the WTP threshold was $100,000/ QALY and $150,000/QALY, respectively. When the cost of atezolizumab was reduced to 65% or 90%, atezolizumab was cost-effective compared with platinum-based chemotherapy at the WTP threshold of $100,000/QALY or $150,000/QALY, respectively. **AUTHORS' CONCLUSION** Atezolizumab was estimated not to be cost-effective compared with platinum-based chemotherapy in the first-line treatment of patients with NSCLC with high PD-L1 expression.	

Evidence Table : **COST-EFFECTIVENESS**
Question : How cost-effective are Immune Checkpoint Inhibitors treatment options for PD-L1 positive advanced non-small cell lung cancer patients ?

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17. Leung JH, Chang CW, Chan AL, et al. **Cost-effectiveness of immune checkpoint inhibitors in the treatment of non-small-cell lung cancer as a second line in Taiwan.** Future Oncol. 2022;18(7):859-870.	**Economic evaluation study** **Objective** To evaluate the cost–effectiveness of immune checkpoint inhibitors versus docetaxel in patients with advanced NSCLC **Methods**: A Markov model was constructed to simulate the clinical outcomes and costs of advanced non-small-cell lung cancer. Clinical outcomes data were derived from randomized clinical trials. Drug acquisition cost and other health resource use were obtained from the claim data of a tertiary hospital and the National Health Insurance. The outcome was an incremental cost–effectiveness ratio expressed as cost per quality-adjusted life year gained. One-way and probabilistic sensitivity analyses were performed to evaluate the uncertainty of the model parameters. **3 health states** - Progression-free disease - Progressed disease - Death **Time horizon**: 10 years **Discount rate** : 3.5% per year **WTP**: NT$2,221,930 per QALY **Perspective** : National Health Insurance Administration (NHIA)		Advanced NSCLC patients, regardless of PD-L1 expression or histology who had experienced disease progression after a platinum-containing systemic therapy. **Clinical data inputs** 1. Checkmate-017, Checkmate-057 for nivolumab versus docetaxel 2. KEYNOTE-010 for pembrolizumab versus docetaxel 3. OAK for atezolizumab versus docetaxel	ICI monotherapy - pembrolizumab - atezolizumab - nivolumab	Docetaxel	-	- In comparison with docetaxel, pembrolizumab was associated with increased costs of NT$396,965 and QALYs by 0.954 in NSCLC populations; ICER was NT$416,102/QALY. - Nivolumab and atezolizumab were associated with increased costs of NT$689,912 and NT$1,028,653, QALYs increased by 0.439 and 0.651. The resulting ICERs for treating patients with nivolumab and atezolizumab compared with docetaxel were NT$1,572,912/QALY and NT$1,580,469/QALY for NSCLC patients. - The incremental cost for nivolumab and atezolizumab were NT$292,947 and NT$631,688, respectively; yet, the incremental QALYs for nivolumab and atezolizumab were lower than that of pembrolizumab. Therefore, nivolumab and atezolizumab were not cost effective compared with pembrolizumab **Sensitivity analysis** Results indicated that three ICIs were considered cost effective regardless of tumour histology or PD-L1 expression status. The acquisition cost of three ICIs and the costs of resource use were the most important parameters that impacted the ICERs. **AUTHORS' CONCLUSION** The use of pembrolizumab, nivolumab and atezolizumab for treating patients with NSCLC was cost effective compared with docetaxel, at the acceptable WTP threshold of NT$2,221,930 per QALY in Taiwan, regardless of histology or PD-L1 expression status.	

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