CoLab Network

Health Technology Review

Overview of Systematic Reviews of Immune Checkpoint Inhibitors in Non–Small-Cell Lung Cancer with Actionable Driver Mutations

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Key Messages

The effectiveness and safety of using immune checkpoint inhibitor monotherapy in patients with previously treated advanced or metastatic non-small cell lung cancer with actionable mutations or chromosomal rearrangements is currently uncertain.

This review aimed to assess the efficacy and safety of immune checkpoint inhibitors in these patients who did not respond well to previous chemotherapy.

We reviewed 13 systematic reviews of randomized controlled trials. The quality assessment of these reviews revealed critical methodological flaws.

All 13 systematic reviews focused on survival and progression-free survival for patients with non-small cell lung cancer and *epidermal growth factor receptor* gene mutations. The systematic reviews generally considered the same set of four clinical trials and did not report on other outcomes or patient groups, except for one review that looked at patients with different levels of anti-programmed death ligand 1 antibody expression.

Overall, the systematic reviews concluded that using immune checkpoint inhibitors alone, as a second-line therapy or beyond, does not significantly improve overall survival and progression-free survival compared to chemotherapy in patients with non-small cell lunger cancer with *epidermal growth factor receptor* gene mutations.

The use of immune checkpoint inhibitors may be more beneficial for patients with high anti-programmed death ligand 1 antibody expression levels. However, there was no evidence on the efficacy and safety in patients with other specific mutations.

The safety of immune checkpoint inhibitors in patients with any mutation remains unknown based on the lack evidence found in the systematic reviews.

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Abbreviations

ALK	Anaplastic Lymphoma Kinase
AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
BRAF	B-Raf proto-oncogene serine/threonine kinase gene
EGFR	epidermal growth factor receptor
IO	immuno-oncology
ICI	immune checkpoint inhibitor
KRAS	Kirsten rat sarcoma
MA	meta-analysis
MD	mean difference
NA	not applicable
NMA	network meta-analysis
NSCLC	non-small-cell lung cancer
PICOS	Population(s), Intervention(s), Comparator(s), Study Design(s)
PD-L1	Anti-programmed death ligand 1 antibodies
PMDE	Post-market drug evaluation
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-analyses, extension for Protocols
PODET	post-market drug evaluation team
QoL	quality of life
RCT	randomized controlled trial
RET	RET proto-oncogene
RIS	research information services
ROS1	ROS proto-oncogene
SRs	systematic reviews

Introduction and Rationale

Background

Lung cancer is the most frequently diagnosed cancer in Canada and the leading cause of cancer-related deaths in males and females,[1] with more than 29,600 new diagnoses (12.5% new cases in males and 13.3% new cases in females) and 21,000 disease-related deaths (24.2% in males and 25.8% in females) projected in 2021.[1] The adjusted 5-year net survival estimate in Canada for all forms of lung cancers is 22%[1] and the anticipated 5-year survival for patients with non–small-cell lung cancer (NSCLC) is approximately 25%, and 7% for patients with stage IV disease.[2] Smoking is an established risk factor for developing lung cancer accounting for more than 72% of newly diagnosed cases in Canada.[1,3] NSCLC is broadly categorized into two subtypes: squamous cell carcinoma and non-squamous cell carcinoma.[4] Squamous cell NSCLC, formerly known as epidermoid carcinoma, typically originates in the larger central airways of the lungs and is strongly associated with a history of smoking.[5] It often presents with symptoms such as coughing, chest pain, and coughing up blood, and is frequently diagnosed at an earlier stage compared to other types of NSCLC. On the other hand, non-squamous NSCLC, including adenocarcinoma and large cell carcinoma, generally occurs peripherally and may present more commonly with symptoms related to peripheral lesions, such as chest pain or pleural effusion, in addition to cough and dyspnea.[6]

Early diagnosis improves prognosis and patient responsiveness to therapy. Diagnosis is based on histology and symptom presentation.[3,7] Patients may experience worsening coughs, chest pain, hemoptysis, malaise, weight loss, dyspnea, and/or hoarseness at clinical presentation or upon chest imaging.[1,3] In advanced or metastatic disease, patients experience additional symptom burdens such as troubled breathing, chronic cough and chest pain, pain in bone or spine, yellowing of the skin or eyes, weakness or numbness of arms or legs, fatigue and unexplained weight loss, depression, insomnia, and pain.[8,9] Staging at diagnosis is key in determining disease prognosis and facilitates treatment selection.[3,9] Late diagnosis is a significant contributing factor to early mortality and is challenging for disease management in real-world practice. Unfortunately, almost 50% of NSCLC diagnoses in Canada are made at stage IV with only about 23.1% of cases diagnosed at early stage I.[1]

The expression of genomic oncogenic driver mutations in tumours is known to be a root factor for oncogenesis in some tumours. In recent years, several pharmacological therapies have been developed to target these mutated, malfunctioning gene products. Predictive drivers identified in recent years include epidermal growth factor receptor *(EGFR)* gene, ROS proto-oncogene *(ROS1)*, kirsten rat sarcoma *(KRAS)* mutations, anaplastic lymphoma kinase *(ALK)* fusions, B-Raf proto-oncogene serine/threonine kinase gene *(BRAF)*, and others. These discoveries greatly influenced treatment strategies that, in practice, improved patient quality of life and increased overall survival for patients.[9-11] Prevalence estimates from studies show that about 1% to 2% of NSCLC cases are *RET* proto-oncogene *(RET)* fusion positive,[12] 1% are *ROS1* fusion positive,[13] 17% have activating mutations in the *EGFR* gene,[14] and 5% have an *ALK* rearrangement.[15,16]

Immune checkpoint inhibitor (ICI) drugs harness the immune system to fight cancer by targeting proteins (PD-1, PD-L1, CTLA-4) that act as checkpoints, allowing T cells to recognize and destroy cancer cells more effectively.[17] They have shown promising results in various cancers, significantly improving survival rates. In NSCLC, PD-L1 levels are crucial as they predict response to ICI drugs like pembrolizumab, nivolumab, and atezolizumab. Higher PD-L1 expression levels indicate better response rates.[18] The ICI drugs approved for the treatment of NSCLC in Canada are presented in Table 1.

Evidence has shown that tumours bearing specific mutations and managed with therapies targeting these mutations at the biochemical level will respond well to treatment. As such, it is widely recommended to first treat tumours bearing actionable mutations with these targeted therapies. This has been translated into CADTH provisional funding algorithms for *ALK*, *EGFR,* and *RET* aberrations in NSCLC.[19-21] Another key finding is that ICI drugs such as PD-1 or PD-L1 blockers exhibit much smaller antitumour activity in cancers with these identified mutations than in their unmutated counterparts.[22-24] Consequently, Health Canada product monographs[25-27] and CADTH algorithms recommend use of ICIs only after prior use of a targeted therapy and a course of platinum-based chemotherapy.[19-21]

Policy Issue

Currently, ICI monotherapy with atezolizumab, nivolumab, or pembrolizumab is indicated for advanced or metastatic NSCLC, regardless of mutational status, following prior chemotherapy. Currently, publications (including systematic reviews (SRs)[28] on this topic, provide no overall consensus on the use of ICIs in the second-line setting or beyond resulting in any substantial benefits to patients with mutated NSCLC, nor is there consensus on how they compare with single-drug nonplatinum chemotherapies, which is a classical option in this setting. Therefore, this review aims to provide a critical overview of the published SRs that compare the efficacy and safety of ICI monotherapy to other chemotherapeutic drugs in patients with

advanced or metastatic NSCLC with specific mutations or chromosomal rearrangements who have experienced previous chemotherapy.

Main Take-Away

There is no consensus on the effectiveness of immune checkpoint inhibitor monotherapy in patients with previously treated advanced or metastatic non-small-cell lung cancer with actionable mutations or chromosomal rearrangements.

Table 1: ICI Drugs for Advanced or Metastatic NSCLC Currently Reimbursed in Canada

Drug (Trade name, Manufacturer)	Presentation (ATC code)	Approved use
Pembrolizumab[29] (Keytruda, Merck)	Solution for infusion 100 mg/4 mL vial (L01FF02)	First-line monotherapy for metastatic NSCLC in adults with PD-L1 expression (TPS ≥ 1%), excluding those with *EGFR* or *ALK* genomic aberrations, and those ineligible for surgery or definitive chemoradiation. Treatment of adults with metastatic squamous NSCLC in combination with carboplatin and either paclitaxel or nab-paclitaxel, without prior systemic chemotherapy treatment for metastatic NSCLC. Monotherapy for metastatic NSCLC in adults whose tumors express PD-L1 (TPS ≥ 1%) and have disease progression on or after platinum-containing chemotherapy. Patients with *EGFR* or ALK genomic tumor aberrations should have received authorized therapy for these aberrations prior to receiving KEYTRUDA®.
Nivolumab[30] (Opdivo, Bristol Myers Squibb)	Intravenous Infusion, 10 mg nivolumab /mL 40 mg and 100 mg single-use vials (L01FF01)	Locally advanced or NSCLC with progression after platinum-based chemotherapy. Patients with *EGFR* or *ALK* genomic tumor aberrations should experience disease progression on a therapy targeting these aberrations before starting OPDIVO.
Atezolizumab[31] (Tecentriq, Roche)	Solution for infusion, 60 mg per mL; 840 mg and 1200 mg single use vial (L01FF05)	As adjuvant treatment following complete resection and no progression after platinum-based adjuvant chemotherapy for adults with Stage II to IIIA* NSCLC, whose tumors have PD-L1 expression on ≥ 50% of tumor cells. As first-line monotherapy for metastatic NSCLC in adults with high PD-L1 expression (PD-L1 stained ≥ 50% of TCs or PD-L1 stained tumor-infiltrating immune cells, covering ≥ 10% of the tumor area), determined by a validated test, and without *EGFR* or ALK genomic tumor aberrations. For the treatment of adult patients with locally advanced or metastatic NSCLC with progression on or after platinum-based chemotherapy. Patients with *EGFR* or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving TECENTRIQ.

ALK = Anaplastic Lymphoma Kinase; *EGFR* = Epidermal Growth Factor Receptor; NSCLC = Non-Small Cell Lung Carcinoma; PD-L1 = Programmed Death-Ligand 1; TPS = Tumor Proportion Score.

Policy Questions

1. How should ICI monotherapies post-chemotherapy be funded in patients with advanced/metastatic NSCLC harboring actionable driver mutations (i.e., ALK, *EGFR*, *ROS1* or *RET* genomic aberrations)?
2. Should all chemotherapy options be exhausted before funding IO monotherapy?

Purpose

To assess the efficacy and safety of immune checkpoint inhibitor treatments as second-line or subsequent monotherapies in patients with NSCLC harboring actionable driver mutations (e.g., ALK, *EGFR*, *ROS1*, or *RET* genomic aberrations), in comparison to traditional chemotherapeutic agents and optimal supportive care.

Research Questions

1. What is the evidence for the clinical efficacy of atezolizumab, nivolumab, and pembrolizumab monotherapy in patients with advanced or metastatic NSCLC with actionable driver mutations that have progressed on prior chemotherapy compared with those who receive single-drug nonplatinum chemotherapy?
2. What is the evidence for the safety of atezolizumab, nivolumab, and pembrolizumab monotherapy in patients with advanced or metastatic NSCLC with actionable driver mutations that have progressed on prior chemotherapy compared with those who receive single-drug nonplatinum chemotherapy?
3. What is the evidence around how the clinical efficacy of atezolizumab, nivolumab, and pembrolizumab may vary by driver mutation?

Main Take-Away

The purpose of this study is to determine the efficacy and safety of immune checkpoint inhibitors in patients with advanced or metastatic non-small-cell lung cancer with actionable driver mutations who did not respond well to previous chemotherapy.

Opportunities for Stakeholder Feedback

Stakeholders were given the opportunity to comment on the proposed project protocol that informed this report and were invited to provide feedback on the draft report.

Protocol Development

The protocol and review followed the methods of the Cochrane Handbook for Systematic Reviews of Interventions[32] and the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) checklist for SRs.[33] The protocol was written a priori, followed throughout the review process and registered in advance through the PROSPERO International Prospective Register of Systematic Reviews (registration number: CRD42024490981). There are no deviations from the protocol to report.

Clinical Review

Preliminary literature assessment revealed that several SRs answering the research questions had been published. Consequently, the research questions were addressed using an overview of SRs.

Literature Search Methods

An experienced medical information specialist developed and tested the search strategies through an iterative process in consultation with the review team. Another senior information specialist peer reviewed the MEDLINE strategy prior to execution using the Peer Review of Electronic Search Strategies (PRESS) Checklist.[34]

Using the multifile option and deduplication tool available on the Ovid platform, we searched Ovid MEDLINE® ALL, Embase Classic+Embase, and the Cochrane Database of Systematic Reviews.

The strategies utilized a combination of controlled vocabulary (e.g., “Carcinoma, Non-Small-Cell Lung,” “Neoplasm Metastasis,” “Antineoplastic Agents, Immunological”) and keywords (e.g., “NSCLC,” “metastatic”, “atezolizumab”). We applied a systematic review filter to the MEDLINE and Embase searches. We adjusted vocabulary and syntax as necessary across the databases. There were no language restrictions, but we limited results to the publication years 2013 to the present. Where applicable, we removed animal-only, conference abstracts, opinion pieces, and other irrelevant publication types. We downloaded and deduplicated the records using EndNote version 9.3.3 (Clarivate Analytics). The complete literature search strategy is presented in

Appendix 1.

Searches were executed on January 26, 2024 and updated monthly until April 24, 2024.

Selection Criteria

The selection criteria employed in this overview is presented in presented in

Table 2. Protocols, conference abstracts, non-English records, and non-systematic reviews were excluded.

Table 2: Selection Criteria

Criteria	Description
Population	Adults with advanced or metastatic NSCLC[a] with *RET* fusion, *ALK* rearrangement, *ROS1* mutation, or *EGFR* mutation that are considered actionable by targeted therapy who have been previously treated with platinum-based chemotherapy[b]. *Subgroups* PD-L1 expression: • less than 1% • 1% and higher • 50% and higher • unknown or unreported
Intervention	Atezolizumab, nivolumab, or pembrolizumab as monotherapy
Comparators	Docetaxel, gemcitabine, or pemetrexed as monotherapy, or best supportive care[c]
Outcomes	At least one of: Efficacy outcomes: • overall survival • progression-free survival • objective response rate • quality of life or health-related quality of life[d] Safety outcomes: • total number of adverse events • immune-mediated adverse events (e.g., immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, skin adverse reactions, and cardiac disorders) • infusion-related adverse events • serious adverse events[e] • withdrawals due to adverse events • mortality
Study designs	Systematic reviews of randomized controlled trials and/or non-randomized studies[f]

ALK = Anaplastic Lymphoma Kinase; *EGFR* = epidermal growth factor receptor; NSCLC = non–small-cell lung cancer; PD-L1 = programmed death cell 1 ligand 1; *RET* = RET proto-oncogene; *ROS1* = ROS proto-oncogene.

[a]This refers to individuals with locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation or who have metastatic NSCLC.

[b]Actionable driver mutations will be considered separately.

[c]Inclusion of best supportive care as defined by study authors. This comparator expanded consideration to patients who may have no current chemotherapy options remaining.

[d]This outcome focused on change in total score. Additional subscale domains were considered when total scores were not reported.

[e]Grade 3 or 4, or adverse events requiring emergency department visit or hospitalization.

[f]SRs of, or including, non-randomized studies were considered for populations or outcomes of interest only when no RCT evidence was available.

Population

The population of interest was adults with advanced or metastatic NSCLC with *RET* fusion, *ALK* rearrangement, *ROS1* mutation, or *EGFR* mutation that are considered actionable by targeted therapy and who have been previously treated with platinum-based chemotherapy. We also considered subgroups within the study populations with levels of PD-L1 expression as follows: less than 1%, 1% and higher, 50% and higher, or unknown levels. If a review included a mixed population, data only pertaining to the population of interest were considered.

Intervention and Comparators

The interventions of interest were atezolizumab, nivolumab, or pembrolizumab as monotherapy. Eligible comparators were docetaxel, gemcitabine, or pemetrexed as monotherapy or best supportive care. We did not limit the inclusion of interventions or comparators based on dose, dosing intervals or duration of treatment.

Outcomes Definition

The efficacy outcomes of interest were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and quality of life (QoL) or health-related quality of life (HRQoL).

The safety outcomes were total number of adverse events (AEs), immune-mediated AEs, infusion-related AEs, serious adverse events (SAEs), withdrawals due to AEs and mortality. Immune-mediated adverse events commonly attributed to ICI drugs are immune-mediated pneumonitis, colitis, hepatitis, endocrinopathies, skin adverse reactions and cardiac disorders. Infusion-related AEs were considered based on author-reported AEs occurring minutes to hours after drug infusion, including broadly described reactions and/or anaphylaxis. Graded AEs as reported by study authors (grade 3 or grade 4), or any AE requiring an emergency department visit or hospitalization were considered SAEs.

During full-text review, records were excluded when outcomes of interest were not reported.

Study Designs

SRs of randomized controlled trials (RCTs) were eligible for inclusion. Reviews of, or including, non-randomized studies (NRS) were considered only when there was no RCT evidence available for a populations or outcome of interest.

Study Selection Process

The study selection process was documented according to guidance from PRISMA.[35] Prior to the screening process, a pilot screening exercise on two included SRs was conducted. Two reviewers screened the studies independently, and all records deemed potentially relevant were obtained in full-text format. Any disagreements were discussed with or adjudicated by a third reviewer. The reviewers were not blinded to study authors or the centre of publication before study selection. Study screening and assessment of eligibility were facilitated and standardized using DistillerSR software. The study selection process was presented using the PRISMA flow chart.

Data Extraction

A standardized data extraction form was developed and reviewed by CADTH and a content expert. One reviewer extracted data and the extraction was audited by a second reviewer. Pilot data extraction was conducted on two of the included SRs, and data extraction forms were optimized before use.

From each SR the following data were extracted:

- Bibliographic information (first author, year, citation)
- Review eligibility criteria
- Search details (dates and limitations)
- Synthesis approach (i.e., descriptive, meta-analysis)
- Included studies (study design, type, and counts)
- Patients included
- Patient characteristics, including relevant mutations, any prognostic factors at baseline (e.g., treatment history, prior use of ICI drug as either targeted or adjuvant therapy, number of previous therapies, stage at diagnosis, smoking history and status at diagnosis, Eastern Cooperative Oncology Group (ECOG) performance status)
- Interventions (doses, intervals, duration)
- Controls (doses, intervals, duration)
- Efficacy outcomes
- Safety outcomes
- Synthesized results as reported, including the descriptive or pooled summary effects of each comparison for each outcome if meta-analysis was conducted (including associated measures of variation or precision if applicable);
- Results from the RCT-level risk of bias assessment
- Authors' conclusions pertinent to outcomes of interest; and
- Funding sources and author declarations.

Additional data to inform the SR quality assessment were also extracted (e.g., reported methods, rationale for review inclusions or limitations). Where other out-of-scope study data were reported in a review, only data for our population, intervention, comparator and outcomes of interest were extracted. Efficacy and safety outcomes were extracted for populations with mutations of interest and for subgroups of these populations reporting PD-L1 expression levels (categorized as less than 1%, 1% and higher, 50% and higher, and unknown or unreported) if such data were provided in each SR.

Data from RCTs included by the SRs was prioritized. Information was only considered from NRS where available and when a unique population or outcome not covered by the RCTs was reported.

Additionally, the overlap of the primary studies in the included SRs (i.e., multiple SRs of the same primary studies) was considered. Any important nuances and/or discrepancies in the outcomes or results reported were descriptively summarized.

Quality Assessment

We used A MeaSurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)[36] to assess the methodological quality of the included SRs. AMSTAR 2 can be applied to SRs including RCTs or NRS. The following elements of the included SRs were assessed: description of the PICO, protocol, and review methodology; rationale behind selecting study design, search strategy, duplication of the data extraction, and study selection process; list of excluded studies; quality and discussion of the risk of bias assessment; funding of the selected studies and meta-analysis; explanation of the heterogeneity; publication bias assessment; and any conflict of interests with the authors of the reviews and funding sources.

One reviewer completed the assessment, and the results were audited by a second reviewer. Any disagreements were resolved by discussion. An overall rating was assessed for each review considering AMSTAR 2 guidance for rating overall confidence in the results of the review.[36] A rating of *High* indicates that the SR provides an accurate and comprehensive summary of the results of the available studies that address the research questions; *Moderate* indicates the SR has more than one weakness but no critical flaws; *Low* indicates one critical flaw and possibly other identified weaknesses; and *Critical*

indicates the SR has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the evidence informing the research questions. For the purposes of these ratings, critical flaws were: Not having registered a protocol prior to commencement of the review, inadequate literature search, lack of justification for excluded studies, and lack of RoB assessment for studies included in the review. The strengths and limitations for each included review were summarized alongside the overall ratings assessed.

For a SR involving a network meta-analysis (NMA), the confidence of the results is dependent not only on the SR methods that can be assessed with the AMSTAR 2, but also, the analytic complexities in estimating specific pairwise effects in the NMA and the assumptions of goodness of fit of the model, homogeneity and consistency need to be assessed.[37]

No de novo risk of bias assessments were conducted for the primary studies included in each review. We summarized the author-assessed results for any reported risk of bias assessment of the eligible RCTs or NRS included in each SR and summarized the reported strengths and limitations. We additionally considered any discrepancies or deficiencies in the risk of bias assessments reported by the authors of the included SRs.

Data Analyses and Synthesis

A descriptive summary of the characteristics of the included reviews was completed. For each population of interest (*RET* gene fusion, *ALK* gene rearrangement, *ROS1* mutation, or *EGFR* gene mutation), results for each efficacy and safety outcome of interest was summarized and synthesized narratively based on the author-reported findings across the SRs. Results are also presented for any reported quantitative syntheses for all outcomes of interest, including all relative or absolute effects. For pairwise meta-analysis (MA) this includes: the model (fixed effects (FE) or random effects (RE) model), the meta-analytic estimates (such as, the hazard ratio (HR) effect estimate and confidence interval (CI)) and measure of heterogeneity (I^2). For network meta-analysis (NMA) this includes: the probabilistic approach (Bayesian), the network meta-analytic estimates based on direct and indirect evidence (such asHR) and mean difference (MD) effect estimates and credible interval (CrI)) and ranking methods such as the surface under the cumulative ranking curve (SUCRA) for a treatment which is a Bayesian summary of the ranking of multiple competing treatments which can be interpreted as the estimated proportion of treatments worse than the treatment of interest. No new quantitative syntheses were planned (e.g., meta-analysis of individual or aggregate study results). Data for each actionable driver mutation were considered separately when summarizing the quantitative results extracted from the included SRs.

Summary of Evidence

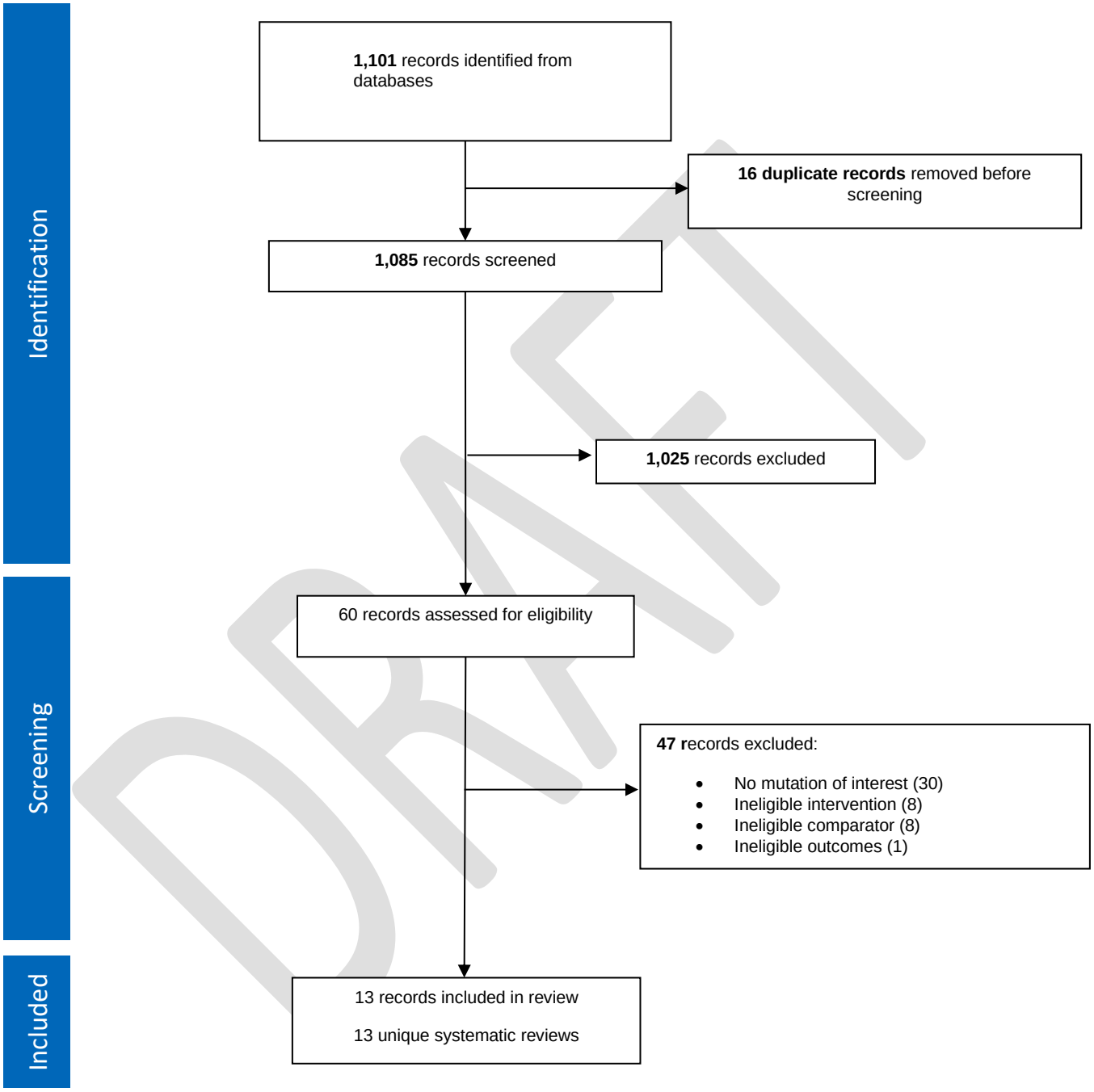
Quantity of Research Available

Main Take-Away

A total of 13 systematic reviews of randomized controlled trials met the final inclusion criteria.

A total of 1,101 records were identified in the literature search. Following screening titles and abstracts, 1,025 records were excluded, and 60 potentially relevant records were retrieved for full-text review. Of these, 47 were excluded for various reasons (Appendix 4, Table 16); and 13 records reporting 13 unique SRs met the inclusion criteria (Figure 1). Details on the included SRs is provided in Table 3.

Figure 1: PRISMA Flow Chart of Selected Reports



Alt text: The PRISMA flow chart depicts the flow of records through the screening and selection process. The figure identifies the number of records screened (1,085 records); the number of full-text reports assessed (60 records), not retrieved (0 records), or excluded (47 records); the number of relevant records included (13 records); and the number of unique studies considered in those records (13 studies).

Summary of Study Characteristics

The study characteristics for the 13 included SRs are summarized in Table 3.

Main Take-Away

All 13 systematic reviews reported overall survival and progression-free survival for patients with non-small-cell lung cancer who were positive for an *epidermal growth factor receptor* gene mutation. The systematic reviews generally considered the same set of clinical trials. No other efficacy or safety outcomes or populations were reported, except for one systematic review that looked at *epidermal growth factor receptor* gene mutation positive patients with different levels of Programmed death-ligand 1(PD-L1) expression. None of the systematic reviews included eligible non-randomized studies.

Study and Patient Characteristics

Description of Systematic Reviews

Of the 13 eligible SRs[38-50], 10 included a meta-analysis[38-46,50] and three included a network meta-analysis.[47,49,48] All included SRs reported RCTs with eligible populations. None of the SRs reported any eligible non-randomized studies including patients of interest.

Broadly, the number of individual RCTs included in the SRs ranged between 3 RCTs and 31 RCTs, however, only a small proportion (i.e., between two and four RCTs per included SR)[51-54] included NSCLC patients with the mutations of interest. The characteristics of the four relevant RCTs reporting patients of interest are described in Appendix 3, Table 12.

While the overall number of NSCLC patients included in the RCTs considered in the SRs was large (range 1,903 to 9,983), the number of patients with one of the eligible mutations was small (range 146 to 272) or not reported at all.[38-50]

Characteristics of Patients Included in the Systematic Reviews

The gender and age of the patients were inconsistently reported.[40-42,46] The SRs broadly included RCTs, reporting patients with a mean age of 60 years or older. The proportion of male patients in the included RCTs ranged from 47.1% male to 82%.[41,42,44,46] In one SR, patients with NSCLC were categorized by patients' lung cancer histology (i.e., nonsquamous or squamous) and further by their PD-L1 expression levels.[49] This review provided the proportion of Asian and non-Asian participants in each group (range 0.8% Asian to 21% Asian), and the proportion of Asian patients was used as a study-level covariate to investigate statistical model fit by authors. The study did not investigate outcomes within this subgroup of patients.

Characteristics of Patients with NSCLC and Mutations of Interest

The 13 SRs included RCTs reporting patients positive for *EGFR* mutations. Of these, 3 SRs noted small proportions of patients positive for *ALK* rearrangement (range 0% to 4%) and no additional details for these patients are reported.[43,45,47] None of the SRs included RCTs which reported patients with *ROS1* mutation or *RET* fusion.[38-50]

The SR-reported patient characteristics for the patients in the included RCTs who had NSCLC and *EGFR* mutation was very limited or non existent.[38-50] The total number of *EGFR*-positive patients in the RCTs included was reported by four SRs (range 168 patients to 272 patients).[39-41,46] None of the included SRs reported any sex or age information for these patients.[38-50]

All 13 included SRs described the patients with *EGFR* mutation as being pre-treated in some way;[38-50] very few reported detail about drugs used in the treatment history.[38-42,44-47,49,50] For example, the treatment characteristics defining the included RCT patient populations may have differentiated these studies as first-line or non-first-line, but the details of the previous treatments received were not reported.[50] One SR considered patients previously treated with tyrosine kinase inhibitors (TKIs).[48] In one SR, the treatment history of two of the four included RCTs was reported to be platinum-based chemotherapy, but the treatment history for the patients in the remaining trials was not reported.[43] Included RCTs in one SR recruited patients treated with second-line ICI monotherapy; however no details on the first line of therapy were given.[49] In three SRs, outcomes of ICI monotherapies as 2nd line or unspecified subsequent lines were analyzed.[42,46,50] Both 2nd- and 3rd-line ICI monotherapies were included in five SRs.[41,44,45,47,48] In four SRs, the patients were described as previously treated but the previous treatment details were not provided.[38-40,43]

One NMA reported the proportion of patients who were identified as Asian in subgroups of participants with *EGFR*-positive status based on histology (squamous/non-squamous) and PD-L1 thresholds of ≥ 5% or < 5% (range 0.8% Asian to 18.8% Asian).

Interventions

The SRs considered at least one of the interventions of interest. All 13 SRs examined nivolumab,[38-50] 12 SRs examined pembrolizumab[38-48,50] and 10 SRs examined atezolizumab.[39,41-48,50]. In all SRs, the interventions included were monotherapy.[38-50]

Eleven SRs pooled the ICI interventions to consider the class effect.[38-46,48,50] Among these, eight SRs considered the class effect of nivolumab, pembrolizumab or atezolizumab,[39,41-46,50] three SRs considered the class effect for nivolumab or pembrolizumab,[38,40,42] and one SR with NMA considered both the class effect of nivolumab, pembrolizumab or atezolizumab and the effect of each intervention individually.[48] One SR considered only the individual effects of nivolumab, pembrolizumab or atezolizumab[47] and one considered nivolumab only in various dosing regimens.[49]

Comparators

All included SRs included RCTs which compared ICI therapy to docetaxel.[38-50] One SR also considered RCT data comparing nivolumab to both pemetrexed and best supportive care (for which no definition was provided).[49] This was the only review to state the dose for the comparator (docetaxel) at frequent low dose, 60 mg/kg, 75 mg/kg and 100 mg/kg; pemetrexed at 500 mg/m^2).[49] No other comparator details were reported. Three SRs involved evidence networks for conducting NMA in which case all pairwise comparisons of the drugs in the network are considered based on direct and indirect evidence.[38-50]

Efficacy Outcomes

The included SRs focused on summarizing two outcomes of interest in the RCTs: OS and PFS.[38-50] All outcomes are for patients with *EGFR* mutation and no other efficacy outcomes for the population of interest were reported. OS was reported in all 13 SRs, but the range of RCTs used for the outcome data (3 RCTs to 4 RCTs) was only mentioned in 11 SRs.[38-46,48,50] PFS was included in four SRs from 2 RCTs.[40,42,45,50] In two SRs, the RCTs used for PFS outcomes were not clear.[47,49]

Safety Outcomes

None of the SRs reported any of the safety outcomes of interest for the included RCTs of ICI monotherapy for NSCLC patients with *EGFR* mutations.[38-50]

Important Subgroups

While many of the SRs considered patients' PD-L1 expression status, only one review reported results for any outcomes of interest in *EGFR*-positive patients. In the review, an NMA model was used to compare the efficacy of nivolumab (3 mg/kg) with docetaxel, best supportive care and pemetrexed in patients with *EGFR*-positive nonsquamous or squamous NSCLC with PD-L1 expression of < 5% or ≥ 5%.[49] No other subgroups of interests were identified across the SRs.

Table 3: Characteristics of Included Systematic Reviews

Systematic Review	Number of primary studies and review method	Patients, mutation type, age, and sex in primary studies	Previous treatment and line of current treatment in the population of interest	Drug comparison[a]	Outcomes (number of RCTs informing the PICO)
Wang, 2016[38]	9 RCTs, MA	Overall: 3,032 Age: NR Sex: NR *EGFR* Positive: NR	Previous treatment: Standard chemotherapy Line: NR	ICI (nivolumab or pembrolizumab) vs. docetaxel[b]	OS (2)

Systematic Review	Number of primary studies and review method	Patients, mutation type, age, and sex in primary studies	Previous treatment and line of current treatment in the population of interest	Drug comparison[a]	Outcomes (number of RCTs informing the PICO)
		Age: NR Sex: NR			
Lee, 2017[39]	3 RCTs, MA	Overall: 1,903 Age: NR Sex: NR *EGFR* Positive: 186 Age: NR Sex: NR	Previous treatment: not specified Line: NR	ICI (atezolizumab or nivolumab or pembrolizumab) vs. docetaxel[b]	OS (3)
Sheng, 2017[40]	14 RCTs, MA	Overall: 2,475 Age: Median 62-63 Sex: NR *EGFR* Positive 168 Age: NR Sex: NR	Previous treatment: not specified Line: NR	ICI (nivolumab or pembrolizumab) vs. docetaxel[c]	OS (2) PFS (2)
Huang, 2018[41]	7 RCTs, MA	Overall: 3,871 Age: < 65 years 53%-58%, one study n/a Sex: women 24%-93%) *EGFR* Positive: 272 Age: NR Sex: NR	Previous treatment: not specified Line: 2nd and 3rd line	ICI (atezolizumab or nivolumab or pembrolizumab) vs. docetaxel[b]	OS (4)
Jiang, 2018[42]	5 RCTs, MA	Overall: 3,025 Age: 61 – 64 years Sex (male): 1,850 (61.16%) *EGFR* Positive: NR Age: 61 – 64 years Sex: NR *ALK*-positive: NR[d] Age: NR Sex: NR	Previous treatment: not specified Line: 2nd line and beyond	ICI (atezolizumab or nivolumab or pembrolizumab) vs. docetaxel[c] ICI (nivolumab or pembrolizumab) vs. docetaxel[c]	OS (3) PFS (2)
Abdel-Rahman, 2018[43,d]	5 RCTs, MA	Overall: 3,013 Age: NR Sex: NR	Previous treatment:	ICI (atezolizumab or nivolumab or pembrolizumab) vs. docetaxel[b]	OS (4)

Systematic Review	Number of primary studies and review method	Patients, mutation type, age, and sex in primary studies	Previous treatment and line of current treatment in the population of interest	Drug comparison[a]	Outcomes (number of RCTs informing the PICO)
		EGFR Positive: NR Age: NR Sex: NR	Platinum-based doublets (2) Treatment history NR (2) Line: NR		
Liu, 2018[44]	5 RCTs, MA	Overall: 2,910 Age: NR Sex (male) 53-82% *EGFR* Positive: 146 Age: NR Sex: NR	Previous treatment: Not specified Line: 2nd and 3rd lines	ICI (atezolizumab or nivolumab or pembrolizumab) vs. docetaxel[b]	OS (3)
Khan, 2018[45d]	7 RCTs, MA	Overall: 3,867 Age: NR Sex: NR *EGFR* Positive: NR Age: NR Sex: NR	Previous treatment: Not specified Line: 2nd and 3rd lines	ICI (atezolizumab or nivolumab or pembrolizumab) vs. docetaxel[c]	OS (3) PFS (2)
Lee, 2018[46]	5 RCTs, MA	Overall: 3,025 Age (≥65 years): 1,302 (43%) Sex (male): 1,425 (47.1%) *EGFR* Positive: 271 Age: NR Sex: NR	Previous treatment: Not specified Line: 2nd line and beyond	ICI (atezolizumab or nivolumab or pembrolizumab) vs. docetaxel[b]	OS (4)
Almutairi, 2019[47,d]	5 RCTs, NMA	Overall: 3,024 Age: NR Sex: NR *EGFR* Positive: NR Age: NR Sex: NR	Previous treatment: Not specified Line: 2nd and 3rd lines	Comparisons:[e] Atezolizumab vs. docetaxel[b] Nivolumab vs. docetaxel[a] Pembrolizumab vs. docetaxel[b]	OS (NR) PFS (NR)
Cavanna, 2019[48]	4 RCTs, MA 4 RCTs, NMA	Overall: 2,753 Age: NR Sex: NR *EGFR* Positive: 272	Previous treatment: TKI Therapy Line: 2nd and 3rd lines	Comparisons:[e] Atezolizumab vs. docetaxel[b] Nivolumab vs. docetaxel[b] Pembrolizumab vs. docetaxel[b] ICI (atezolizumab or nivolumab or pembrolizumab) vs. docetaxel[b]	OS (4)

Systematic Review	Number of primary studies and review method	Patients, mutation type, age, and sex in primary studies	Previous treatment and line of current treatment in the population of interest	Drug comparison[a]	Outcomes (number of RCTs informing the PICO)
		Age: NR Sex: NR			
Vickers, 2019[49]	31 RCTs[f], NMA	Overall: 9,983 Age: NR Sex: NR *EGFR* Positive: NR Age: NR Sex: NR	Previous treatment: Not specified Line: 2nd line	Comparisons:[e] • Nivolumab vs. best supportive care[b, g] • Nivolumab vs. docetaxel (frequent low dose)[b] • Nivolumab vs. docetaxel (60 mg/m² every 3 wks)[b] • Nivolumab vs. docetaxel (75 mg/m² every 3 wks)[b] • Nivolumab vs. docetaxel (100 mg/m² every 3 wks)[b] • Nivolumab vs. pemetrexed (500 mg/m²)[b] • Nivolumab vs. docetaxel (75 mg/m² every 3 wks)[h]	OS (NR) PFS (NR)
An, 2021[50]	12 RCTs, MA	Overall: 7,442 Age: NR Sex: NR *EGFR* Positive: NR Age: NR Sex: NR	Previous treatment: Not specified Line: 2nd line and beyond	ICI (atezolizumab or nivolumab or pembrolizumab) vs. docetaxel[b] ICI (nivolumab or pembrolizumab) vs. docetaxel[b]	OS (3) PFS (2)

ALK = anaplastic lymphoma kinase; chemo = chemotherapy; *EGFR* = epidermal growth factor receptor; FDA = Food and Drug Administration; ICIs = immune checkpoint inhibitor monotherapies; MA = meta-analysis; NMA = network meta-analysis; NR = not reported; OS = Overall survival; PICO = Participants, Intervention, Controls, Outcomes; PFS = Progression-free survival; SR = systematic review; RCTs = randomized control trials; vs = versus; wks = weeks.

[a]The listed drug comparisons all align with the pre-specified interventions and comparators outlined in the PICO framework.

[b]Fixed effects model.

[c]Random effects model.

[d]The primary studies described data regarding *ALK*, but none of them stratified OS or PFS data based on *ALK* status.

[e]In the NMA, pairwise comparisons between any drug and any comparator in the evidence network are available; Here, we focus only on pairwise comparisons involving the interventions and comparators of interest.

[f]NMA of several RCTs but it was not possible to ascertain which RCTs were used for the analyses.

[g]Best supportive care is not defined or described.

[h]Using the random effect model for significant ($P < 0.05$) results were given for nivolumab vs docetaxel (75 mg/m² every 3 weeks) per subgroup.

Overlap of RCTs in the Systematic Reviews

The overlap of the RCTs included by the SRs reporting efficacy outcomes of interest is detailed in Table 13 and Table 14 (Appendix 2). A total of four unique RCTs[51-54] including patients with NSCLC and a mutation of interest were identified from the trials included by the SRs. All four compared an ICI monotherapy to docetaxel. The CheckMate057[51] trial assessed nivolumab, the Keynote-010[54] trial assessed pembrolizumab and the OAK[53] and POPLAR trials assessed atezolizumab.

Overall survival for nivolumab from the CheckMate057[51] trial was considered in 10 SRs[38-44,46,48,50], for pembrolizumab from the Keynote-010[54] trial in nine SRs[38,40-50] and for atezolizumab from the OAK[53] trial in 5 SRs[41,43-46,48,49] from the POPLAR[52] trial in eight SRs.[39,41,43,45-49]

Fewer RCTs reported PFS. The CheckMate057[51] and OAK[53] trials both reported PFS for nivolumab and pembrolizumab and were considered by three SRs,[40,42,50]

The RCTs informing the analyses in two SRs[45,47] and one NMA[49], were not reported. Therefore, RCT overlap assessment not possible. No safety outcomes specific to the population of interest were assessed in any SR and so overlap assessment was not feasible.[38-50]

Data Analysis and Synthesis

Main Take-Aways

Overall, the systematic reviews of randomized controlled trials concluded that using ICIs alone, as second-line therapy or beyond, does not significantly benefit patients with NSCLC and *EGFR* gene mutations when compared to chemotherapy. Limited data are available for comparisons of nivolumab to best supportive care and pemetrexed in patients with NSCLC and *EGFR* gene mutations.

ICIs may be more beneficial in patients with *EGFR* mutations with high PD-L1 expression levels (PD-L1 $\geq$ 5% rather than < 5%).

The results from all included reviews should be interpreted with caution due to critical flaws in the methodology and reporting. The results for clinical efficacy in populations with *EGFR* may not represent an accurate and comprehensive summary of the available randomized controlled trials.

Efficacy: Overall Survival

The results of the pairwise MA and NMA for OS for ICI monotherapy compared to docetaxel in patients with NSCLC and an *EGFR* mutation are described below. A detailed summary of these results is presented in

Table 4.

Meta-analysis

In the pairwise MAs for OS, the different ICI monotherapies were combined and considered as a single class of ICI drugs and compared to docetaxel. No dose was provided for any of the drugs assessed.

ICI (Nivolumab, Pembrolizumab) Monotherapy Versus Docetaxel

Two SRs compared nivolumab or pembrolizumab monotherapy as an ICI drug class to docetaxel.[38,40] Both SR considered the same two RCTs (CheckMate 057, Keynote 010) and each found no statistically significant difference for OS (HR = 1.05, 95% CI 0.69 to 1.59).

ICI (Atezolizumab, Nivolumab, Pembrolizumab) Monotherapy Versus Docetaxel

Nine SRs compared atezolizumab, nivolumab or pembrolizumab monotherapy as an ICI drug class to docetaxel.[43] Four of these SRs considered the same four RCTs (CheckMate 057, Keynote 010, POPLAR, OAK) and each found no significant difference for OS (e.g., HR=1.11, 95% CI 0.80 to 1.53).[43,46,48] Not including the POPLAR RCT, three SRs considered the same three RCTs (CheckMate 057, Keynote 010, OAK) and also found similar results of no significant difference for OS (HR = 1.12, 95% CI 0.80 to 1.56).[39,42,50] A SR including the RCTs CheckMate 057, Keynote 010, POPLAR found no statistically significant difference for OS (HR = 1.05, 95% CI, 0.70 to 1.55),[39] while another SR arrived at a different conclusion, without identifying the included RCTs (HR = 1.14, 95% CI 0.85 to 1.53).[45]

Network Meta-analysis

In two NMAs, individual ICI drugs were compared to docetaxel as the reference node. None of the NMAs reporting OS considered best supportive care or pemetrexed. No dose was provided for any of the drugs assessed.

Individual ICI Monotherapies Versus Docetaxel

In one SR/NMA which used a Bayesian model, results indicated no statistically significant OS benefit for patients with *EGFR* mutated NSCLC taking atezolizumab (HR = 1.25, 95% credible interval (CrI), 0.71 to 2.18), nivolumab (HR = 1.18, 95% CrI, 0.69 to 1.99) or pembrolizumab (HR = 0.87, 95% CrI, 0.45 to 1.70) when compared to docetaxel.[47]

A second NMA reported SUCRA treatment rankings for OS and found that docetaxel ranked higher than the other treatments (60%) followed by pembrolizumab (48%), atezolizumab (46%) and nivolumab (45.6%) in patients of NSCLC with positive *EGFR* mutation. The hazard ratios were not reported.[48]

Table 4: Results by Systematic Review for Overall Survival

Systematic Review	Included RCTs	Comparison[a,b] (n)	Result HR, 95% CI/CrI, I^2
Meta-analysis			
ICI (Nivolumab, Pembrolizumab) Monotherapy Versus Docetaxel			
Wang, 2016[38]	CheckMate 057, Keynote 010	ICI vs. docetaxel (n = NR)[c]	HR = 1.05 95% CI, 0.69 to 1.59 I^2 = 0%
Sheng, 2017[40]	CheckMate 057, Keynote 010	ICI vs. docetaxel (n = 168)[d]	HR = 1.05, 95% CI, 0.69 to 1.59 I^2 = NR
ICI (Atezolizumab, Nivolumab, Pembrolizumab) Monotherapy Versus Docetaxel			
Abdel-Rahman, 2018[43]	CheckMate 057, Keynote 010, POPLAR, OAK	ICI vs. docetaxel (n = NR)[c]	HR = 1.11 95% CI, 0.80 to 1.53 I^2 = 0%
Lee, 2018[46]	CheckMate 057, Keynote 010, POPLAR, OAK	ICI vs. docetaxel (n = 271)[c]	HR = 1.11 95% CI, 0.80 to 1.53 I^2 = 0%
Cavanna, 2019[48]	CheckMate 057, Keynote 010, POPLAR, OAK	ICI vs. docetaxel (n = 272)[d]	HR = 1.12 95% CI, 0.85 to 1.38 I^2 = NR
Huang, 2018[41]	CheckMate 057, Keynote 010, POPLAR, OAK	ICI vs. docetaxel (n = 272)[c]	HR = 1.12 95% CI, 0.80 to 1.53 I^2 = 0%
Liu, 2018[44]	CheckMate 057, Keynote 010, OAK	ICI vs.docetaxel (n = 253)[c]	HR = 1.11 95% CI, 0.80 to 1.55 I^2 = 0%
An, 2021[50]	CheckMate 057, Keynote 010, OAK	ICI vs. docetaxel (n = NR)[c]	HR = 1.12, 95% CI, 0.80 to 1.56 I^2 = 0%
Lee, 2017[39]	CheckMate 057, Keynote 010, POPLAR	ICI vs. docetaxel (n = 186)[c]	HR = 1.05 95% CI, 0.70 to 1.55 I^2 = 0.80%,

Systematic Review	Included RCTs	Comparison[a,b] (n)	Result HR, 95% CI/CrI, I^2
Jiang, 2018[42]	CheckMate 057, Keynote 010, OAK	ICI vs. docetaxel (n = NR)[d]	HR = 1.12 95% CI, 0.80 to 1.56 I^2 = 0%;
Khan, 2018[45]	NR	ICI vs. docetaxel (n = NR)[d]	HR = 1.14 95% CI, 0.85 to 1.53 I^2 = NR
Network meta-analysis			
Almutairi, 2019[47]	RCTs in the evidence network for NMA CheckMate 057, Keynote 010, POPLAR, OAK	Atezolizumab vs. docetaxel (n = NR)[c]	HR = 1.25 95% CrI, 0.71 to 2.18
		Nivolumab vs. docetaxel (n = NR)[c]	HR = 1.18 95% CrI, 0.69 to 1.99
		Pembrolizumab vs. docetaxel (n = NR)[c]	HR = 0.87 95% CrI, 0.45 to 1.70
Cavanna, 2019[48]	RCTs in the evidence network for NMA CheckMate 057, Keynote 010, POPLAR, OAK	Atezolizumab vs. nivolumab vs. pembrolizumab vs. docetaxel (n = 272)[c]	SUCRA- treatment ranking:[e] Docetaxel (SUCRA=60%) Pembrolizumab (SUCRA=48%) Atezolizumab (SUCRA=46%) Nivolumab (SUCRA=45.6%)

CI = confidence interval; CrI = credible interval; HR = hazard ratio; I2 = I-square statistic; NR = not reported; n= number of patients; RCTs = randomized control trials; SR = systematic review; ICI = immune checkpoint inhibitor; SUCRA = surface under the cumulative ranking; vs = versus.

[a]Doses were not reported in any of the SRs.

[b]Two or more ICI are considered one class and compared with docetaxel.

[c]Fixed effects model.

[d]Random effects model.

[e]Credible intervals not reported.

Efficacy: Progression-free Survival

The results for PFS for ICI monotherapy compared to docetaxel in patients with NSCLC and *EGFR* mutation are described below. A detailed summary of these results is presented in Table 5.

Meta-analysis

In the pairwise MAs for PFS, the different ICI monotherapies were combined and considered as a single class of ICI drugs in four SRs.[40,42,45,50]. No dose was provided for any of drugs assessed.

ICI (Nivolumab, Pembrolizumab) Monotherapies Versus Docetaxel

Three SRs compared nivolumab or pembrolizumab monotherapy as an ICI drug class to docetaxel.[40,42,50] All three SRs considered the same two RCTs (CheckMate 057, Keynote 010), and each found that these ICI drugs were inferior to docetaxel in improving PFS (HR =1.57, 95% CI, 1.06 to 2.32).

ICI (Atezolizumab, Nivolumab, Pembrolizumab) Monotherapies Versus Docetaxel

One SR compared atezolizumab, nivolumab or pembrolizumab as an ICI drug class to docetaxel.[45] This SR did not identify the included RCTs and found that these ICI drugs were inferior to docetaxel in improving PFS(HR = 1.57, 95% CI, 1.07 to 2.3).[45]

Network Meta-analysis

Individual ICI Monotherapies Versus Docetaxel

In one SR, an NMA model was used to compare ICI drugs, nivolumab and pembrolizumab individually to docetaxel as the reference node.[47] Results for nivolumab (HR = 1.46, 95% CrI, 0.90 to 2.36) and pembrolizumab (HR = 1.79, 95% CrI, 0.94 to 3.41) showed no statistically significant improvement in PFS when compared individually to docetaxel.[47] Furthermore, using SUCRA, docetaxel ranked higher (SUCRA = 89%) than both the individual drugs in improving PFS.[47]

Table 5: Results by Systematic Review for Progression-free Survival

Systematic Review	Included RCTs	Comparisons (n)	Result HR, 95% CI/CrI, I^2
Meta-analysis			
ICI (Nivolumab, Pembrolizumab) Monotherapies Versus Docetaxel			
An, 2021[50]	Checkmate 057, Keynote 010	ICI vs. docetaxel (n =NR)[a, b]	HR =1.57 95% CI, 1.06 to 2.32 I^2 = 0%
Sheng, 2017[40]	Checkmate 057, Keynote 010	ICI vs. docetaxel (n = 168 [b, c]	HR = 1.57 95% CI, 1.07 to 2.31 I^2 = NR
Jiang, 2018[42]	Checkmate 057, Keynote 010	ICI vs. docetaxel (n =NR)[b, c]	HR = 1.57 95% CI, 1.07 to 2.31 I^2 = 0%;
ICI (Atezolizumab, Nivolumab, Pembrolizumab) Monotherapies Versus Docetaxel			
Khan, 2018[45]	NR	Atezolizumab, nivolumab, pembrolizumab vs. docetaxel (n =NR)[b, c, d]	HR = 1.57 95% CI, 1.07 to 2.31 I^2 = NR
Network meta-analysis			
Almutairi, 2019 [47]	RCTs in the evidence network for NMA CheckMate 057, Keynote 010	Nivolumab vs. docetaxel (n =NR)[a, e]	HR = 1.46 95% CrI, 0.90 to 2.36
		Pembrolizumab vs docetaxel (n =NR)[a,e]	HR = 1.79 95% CrI, 0.94 to 3.41

CI = confidence interval; CrI = credible interval; HR = hazard ratio; ICI = immune checkpoint inhibitor; I^2 = I-square statistic; NR = not reported; n= number of patients; RCTs = randomized control trials; SR = systematic review; vs = versus.

[a]Fixed effects model.

[b]Two or more ICI were pooled as one class and compared with docetaxel. [c] Random effects model.

[d] The RCTs included in the analysis were not specified.

[e]Docetaxel ranked higher than both nivolumab and pembrolizumab (SUCRA for docetaxel: 89%)

Important Subgroups

One SR used an NMA model to assess subgroups based on PD-L1 expression level in several included RCTs of ICI used to treat squamous and non-squamous NSCLC in patients with *EGFR* mutation.[49] PD-L1 subgroups were categorized based on expression levels of < 5% and ≥ 5%.[49]. In the NMA for OS, nivolumab (3 mg/kg) was compared with best supportive care, various doses of docetaxel, and 500 mg/m^2 pemetrexed. For PFS, nivolumab (3 mg/kg) was compared with various doses of docetaxel, and 500 mg/m^2 pemetrexed.

Overall survival with PD-L1 expression levels of < 5% and ≥ 5%

Non-squamous NSCLC

Results for OS in the subgroup of patients with non-squamous NSCLC are provided in Table 6. In patients with non-squamous NSCLC, regardless of the PD-L1 expression levels, nivolumab was more effective in improving OS when compared to best supportive care for PD-L1 < 5% and PD-L1 ≥ 5%.[49] Among patients with PD-L1 < 5%, there was no significant improvement in OS observed with nivolumab compared to docetaxel at frequent low dose, 60 mg/kg, 75 mg/kg or 100 mg/kg.[49] However, in patients with PD-L1 ≥ 5% nivolumab was more effective than docetaxel at frequent low doses, 60 mg/kg, 75 mg/kg, or 100 mg/kg.[49] Similarly, compared to 500 mg/m^2 pemetrexed, nivolumab was more effective in patients with PD-L1 ≥ 5 but not in patients with PD-L1 < 5%.[49]

Table 6: Subgroup Results for Overall Survival for Patients with Non-Squamous NSCLC

Systematic review	Included RCTs	Comparison	PD-L1 expression	Result
Mean Overall Survival Time[a]				**MD, 95%CrI (months)**
Vickers, 2019[49]	RCTs included in the NMA[b]	Nivolumab 3 mg/kg vs best supportive care	PDL-1 < 5%	MD = 8.6 95% CrI, 3.5 to 13.9
			PD-L1 ≥ 5%	MD = 20.0 95% CrI, 11.8 to 31.2
		Nivolumab 3 mg/kg vs docetaxel frequent low-dose	PDL-1 < 5%	MD = 3.3 95% CrI, -0.5 to 7.9
			PD-L1 ≥ 5%	MD = 14.8 95% CrI, 7.1 to 25.8
		Nivolumab 3 mg/kg vs docetaxel 60 mg/kg every 3 weeks	PDL-1 < 5%	MD = 2.4 95% CrI, -1.4 to 6.9
			PD-L1 ≥ 5%	MD = 13.8 95% CrI, 6.3 to 24.8
		Nivolumab 3m/kg vs docetaxel 75 mg/kg every 3 weeks	PDL-1 < 5%	MD = 1.5 95% CrI, -1.9 to 5.9

Systematic review	Included RCTs	Comparison	PD-L1 expression	Result
			PD-L1 ≥ 5%	MD = 12.9 95% CrI, 5.6 to 23.8
		Nivolumab 3 mg/kg vs docetaxel 100 mg/kg every 3 weeks	PDL-1 < 5%	MD = 0.4 95% CrI, -4.3 to 5.4
			PD-L1 ≥ 5%	MD = 11.7 95% CrI, 4.1 to 23.0
		Nivolumab 3 mg/kg vs pemetrexed 500 mg/m²	PDL-1 < 5%	MD = -0.6 95% CrI, -5.3 to 4
			PD-L1 ≥ 5%	MD = 10.8 95% CrI, 3.1 to 21.9
Probability of Survival[c]				**HR, 95% CrI[d, e]**
Vickers, 2019[49]	RCTs included in the NMA[b]	Nivolumab 3 mg/kg vs docetaxel 75 mg/kg every 3 weeks	PD-L1 < 5%	NR
			PD-L1 ≥ 5%	HR = 12.5 95% CrI, 4.8 to 23.9

CrI = credible interval; HR = hazard ratio; I^2 = I-square; n= number of patients; MD = mean difference; PD-L1 = programmed death ligand 1; RCTs = randomized control trials; NMA = network meta-analysis; vs = versus.

[a]Mean survival time is the area under the probability of survival curve with a horizon of 60 years.

[b]31 RCTs identified in the overall evidence network for the NMA but unspecified RCTs identified for the subgroup analysis for *EGFR* positive.

[c]Time to event (i.e., death or progression) - random effects model.

[d]Random effects model representing results with a significant (P < 0.05) benefit over single-agent docetaxel (75 mg/m²) were reported.

[e]HR > 1 indicates greater probability of overall survival for nivolumab

Squamous NSCLC

Results for OS in the subgroup of patients with squamous NSCLC are provided in Table 7. In patients with squamous NSCLC, regardless of the PD-L1 expression levels (PD-L1 < 5% or PD-L1 ≥ 5%), nivolumab was more effective in improving OS than best supportive care.[49] When compared to frequent low doses of docetaxel, 60 mg/kg or 75 m/kg nivolumab was more effective regardless of the PD-L1 levels.[49] However, there was no significant difference between nivolumab and 100 mg/kg docetaxel.[49]

Table 7: Subgroup Results for Overall Survival for Patients with Squamous NSCLC

Systematic review	Included RCTs	Comparison	PD-L1 expression	Result
Mean Overall Survival Time[a]				**MD, 95%CrI (months)**
Vickers, 2019[49]	RCTs included in the NMA[b]	Nivolumab 3 mg/kg vs best supportive care	PDL-1 < 5%	MD = 11.8 95% CrI, 6.1 to 19.1
			PD-L1 ≥ 5%	MD = 14.2 95% CrI, 7.0 to 24.4

Systematic review	Included RCTs	Comparison	PD-L1 expression	Result
		Nivolumab 3 mg/kg vs docetaxel frequent low-dose	PDL-1 < 5%	MD = 7.1 95% CrI, 2.1 to 14.1
			PD-L1 ≥ 5%	MD = 9.5 95% CrI, 3.0 to 19.5
		Nivolumab 3 mg/kg vs docetaxel 60 mg/kg every 3 weeks	PDL-1 < 5%	MD = 6.3 95% CrI, 1.4 to 13.1
			PD-L1 ≥ 5%	MD = 8.7 95% CrI, 2.3 to 18.7
		Nivolumab 3 mg/kg vs docetaxel 75 mg/kg every 3 weeks	PDL-1 < 5%	MD = 5.5 95% CrI, 0.7 to 12.4
			PD-L1 ≥ 5%	MD = 8.0 95% CrI, 1.6 to 17.8
		Nivolumab 3 mg/kg vs docetaxel 100 mg/kg every 3 weeks	PDL-1 < 5%	MD = 4.5 95% CrI, -1.1 to 11.7
			PD-L1 ≥ 5%	MD = 7.0 95% CrI, 0.0 to 17.0
		Nivolumab 3 mg/kg vs pemetrexed 500 mg/m²	PDL-1 < 5%	MD = 9.2 95% CrI, 4.0 to 16.5
			PD-L1 ≥ 5%	MD = 11.6 95% CrI, 4.7 to 21.9
Probability of Survival[c]				**HR, 95% CrI[d, e]**
Vickers, 2019[49]	RCTs included in the NMA[b]	Nivolumab 3 mg/kg vs docetaxel, 75 mg/kg every 3 weeks	PDL-1 < 5%	HR = 5.7 95% CrI, 0.6 to 13.1
			PD-L1 ≥ 5%	HR = 7.9 95% CrI, 1.4 to 18.1

CrI = credible interval; HR = hazard ratio; I^2 = I-square; n= number of patients; MD = mean difference; PD-L1 = programmed death ligand 1; RCTs = randomized control trials; NMA = network meta-analysis; vs = versus.

[a]Mean survival time is the area under the probability of survival curve with a horizon of 60 years.

[b]31 RCTs identified in the overall evidence network for the NMA but unspecified RCTs identified for the subgroup analysis for *EGFR* positive.

[c]Time to event (i.e., death or progression) - random effects model.

[d]Random effects model representing results with a significant (P < 0.05) benefit over single-agent docetaxel (75 mg/m²) were reported.

[e]HR > 1 indicates greater probability of overall survival for nivolumab

Progression-Free Survival with PD-L1 expression levels of < 5% and ≥ 5%

Non-squamous NSCLC

Results for PFS in the subgroup of patients with non-squamous NSCLC are provided in Table 8. In patients with non-squamous NSCLC with *EGFR* mutation and PD-L1 ≥ 5%, nivolumab was more effective in improving PFS when compared to docetaxel at 60 mg/kg, 75 mg/kg or 100 mg/kg.[49] However, no significant differences were observed among patients with non-squamous NSCLC, *EGFR* mutation, and PD-L < 5% when nivolumab was compared with docetaxel at 60 mg/kg, 75 mg/kg or 100 mg/kg.[49] Similarly, when compared to pemetrexed, nivolumab was more effective in improving PFS with PD-L1 ≥ 5% but not with PD-L < 5%.[49]

Table 8: Subgroup Results for Progression-free Survival for Patients with Non-Squamous NSCLC

Systematic review	Included RCTs	Comparison	PD-L1 expression	Result
Mean Progression-free Survival Time[a]				**MD, 95%CrI (months)**
Vickers, 2019[49]	RCTs included in the NMA[b]	Nivolumab 3 mg/kg vs docetaxel 60 mg/kg every 3 weeks	PDL-1 < 5%	MD = -0.6 95% CrI, -2.7 to 1.8
			PD-L1 ≥ 5%	MD = 5.1 95% CrI, 1.9 to 8.7
		Nivolumab 3 mg/kg vs docetaxel 75 mg/kg every 3 weeks	PDL-1 < 5%	MD = -0.7 95% CrI, -1.9 to 1.1
			PD-L1 ≥ 5%	MD = 5.0 95% CrI, 2.2 to 8.2
		Nivolumab 3 mg/kg vs docetaxel 100 mg/kg every 3 weeks	PDL-1 < 5%	MD = -0.7 95% CrI, -2.3 to 1.3
			PD-L1 ≥ 5%	MD = 5.0 95% CrI, 2.1 to 8.3
		Nivolumab 3 mg/kg vs pemetrexed 500 mg/m²	PDL-1 < 5%	MD = -1.1 95% CrI, -3.3 to 1.1
			PD-L1 ≥ 5%	MD = 4.6 95% CrI, 1.2 to 8.1
Probability of Survival[c]				**HR, 95% CrI[d,e]**
Vickers, 2019[49]	RCTs included in the NMA[b]	Nivolumab 3 mg/kg vs docetaxel 75 mg/kg every 3 weeks	PD-L1 < 5%	NR
			PD-L1 ≥ 5%	HR = 4.4 95% CrI, 0.8 to 7.6

CrI = credible interval; HR = hazard ratio; I^2 = I-square; n= number of patients; MD = mean difference; PD-L1 = programmed death ligand 1; RCTs = randomized control trials; NMA = network meta-analysis; vs = versus.

[a]Mean survival time is the area under the probability of survival curve with a horizon of 60 years.

[b]30 RCTs identified in the overall evidence network for the NMA but unspecified RCTs identified for the subgroup analysis for *EGFR* positive.

[c]Time to event (i.e., death or progression) - random effects model.

[d]Random effects model representing results with a significant (P < 0.05) benefit over single-agent docetaxel (75 mg/m^2) were reported.

[e]HR > 1 indicates greater probability of PFS for nivolumab.

Squamous NSCLC

Results for PFS in the subgroup of patients with squamous NSCLC are provided in Table 9. In patients with squamous NSCLC with *EGFR* mutation and PD-L1 > 5%, nivolumab was more effective in improving PFS when compared to docetaxel at 60 mg/kg, 75 mg/kg or 100 mg/kg.[49] However, no significant differences were observed among patients with squamous NSCLC, *EGFR* mutation, and PD-L1 < 5% when nivolumab was compared with docetaxel at 60 mg/kg, 75 mg/kg or 100 mg/kg.[49] Similarly, when compared to pemetrexed, nivolumab was more effective in improving PFS with PD-L1 ≥ 5% but not with PD-L1 < 5%.[49]

Table 9: Subgroup Results for Progression-free Survival for Patients with Squamous NSCLC

Systematic review	Included RCTs	Comparison	PD-L1 expression	Result
Mean Progression-free Survival Time[a]				**MD, 95%CrI (months)**
Vickers, 2019[49]	RCTs included in the NMA[b]	Nivolumab 3 mg/kg vs docetaxel 60 mg/kg every 3 weeks	PDL-1 < 5%	MD = 2.8 95% CrI, -0.4 to 6.3
			PD-L1 ≥ 5%	MD = 5.7 95% CrI, 1.7 to 10.5
		Nivolumab 3 mg/kg vs docetaxel 75 mg/kg every 3 weeks	PDL-1 < 5%	MD = 2.6 95% CrI, 0.0 to 5.8
			PD-L1 ≥ 5%	MD = 5.7 95% CrI, 1.8 to 10.1
		Nivolumab 3 mg/kg vs docetaxel 100 mg/kg every 3 weeks	PDL-1 < 5%	MD = 2.6 95% CrI, -0.1 to 6.1
			PD-L1 ≥ 5%	MD = 5.6 95% CrI, 1.6 to 10.1
		Nivolumab 3 mg/kg vs pemetrexed 500 mg/m^2	PDL-1 < 5%	MD = 4.3 95% CrI, 0.6 to 8.0
			PD-L1 ≥ 5%	MD = 7.2 95% CrI, 2.7 to 12.1
Probability of Survival[c]				**HR, 95% CrI[d, e]**
Vickers, 2019[49]	RCTs included in the NMA[b]	Nivolumab 3 mg/kg vs docetaxel 75 mg/kg every 3 weeks	PDL-1 < 5%	HR = 2.7 95% CrI, 0.1 to 6.2
			PD-L1 ≥ 5%	HR = 5.4 95% CrI, 1.6 to 9.6

CrI = credible interval; HR = hazard ratio; I^2 = I-square; n= number of patients; MD = mean difference; PD-L1 = programmed death ligand 1; RCTs = randomized control trials; NMA = network meta-analysis; vs = versus.

[a]Mean survival time is the area under the probability of survival curve with a horizon of 60 years.

[b]30 RCTs identified in the overall evidence network for the NMA but unspecified RCTs identified for the subgroup analysis for *EGFR* positive.

[c]Time to event (i.e., death or progression) - random effects model.

[d]In this SR, for random effects model, only results with a significant (P < 0.05) benefit over single-agent docetaxel (75 mg/m^2) were reported.

[e]HR > 1 indicates greater probability of PFS for nivolumab

Safety: All Outcomes

Although some of the included SRs assessed safety outcomes[38,40,42,44,45,47,50], none considered or reported AEs and SAEs specific to patients with NSCLC and the gene mutations of interest for this review. It is unclear if any of the RCTs included in the SRs report safety outcomes stratified for patients with the *EGFR* gene mutation.

Summary of Authors' Critical Appraisal

Ten SRs assessed the risk of bias for the RCTs included in the review and, of these, seven reported results for the assessments. Three SRs did not report any critical appraisal.[38,39,48]

Risk of bias results overall and across domains generally assessed the RCTs included by the SRs to be at low risk of bias for most domains assessed, although lack of blinding of participants and personnel (performance bias) and outcome status (detection bias) was a common limitation noted in seven SRs for the included RCTs (ratings were high or unclear for associated risk of bias).

Summary of Publication Bias Assessment

Six SRs considered publication bias across the RCTs included. No substantial publication bias was reported.[40-42,44,46,50]

Summary of Authors' Conclusions

Overall conclusions relevant to the populations of interest by SR are summarized in Table 15Table 15 (Appendix 3). Of the 13 SRs included, nine reported conclusions for patients with NSCLC and *EGFR* gene mutation for either OS (n=8)[38-41,44,46,48,50] or PFS (n=1).[42]

Author conclusions for OS were consistent across all reviews that ICI therapy did not result in OS benefits for patients with NSCLC and *EGFR* gene mutation, even when OS benefits were seen in broader populations or other subpopulations.[38-41,44,46,48,50]

In a single SR reporting conclusions based on PFS, the authors deduced that ICI therapy did not result in any benefits for PFS in patients with NSCLC and *EGFR* gene mutation.[42]

Summary of Critical Appraisal of Systematic Reviews

The quality assessment of the 13 included SRs, conducted with AMSTAR 2, is presented in Table 10. All SRs were assessed to be critically low in methodological quality due to at least two critical flaws (range 2 critical flaws to 3 critical flaws) related to not having registered a protocol prior to the commencement of the reviews, adequacy of the literature search, a lack of justification for RCTs excluded, and/or a lack of RoB assessment for studies included in the review. The reporting quality of the methods and results varied greatly and impacted the ratings for each item assessed using AMSTAR 2. According to guidance from AMSTAR2, more than one critical flaw in a SR indicates that the review should not be relied on to provide an accurate and comprehensive summary of the available studies.

All included SRs had a clearly defined PICO.[38-50] Only one SR had its protocol registered before the commencement of the review process, however this SR was assessed to have a deviation from the protocol which was not justified (omission of a planned outcome: objective response rate).[49] None of the included SRs justified their selection of the study designs (RCTs) for inclusion.[38-50] Some details regarding the search strategy were provided in ten out of the 13 included SRs but none of them

included a comprehensive summary of methods applied or reported searching references from the bibliographies of the included RCTs.[38,39,41,42,44-46,48-50] Three SRs did not report any details of search methodology.[40,43,47]

In six reviews, the study selection was carried out in duplicate by two reviewers[40,42,45-47,49] while the remaining SRs did not provide any details about the selection process.[38,39,43,48,50] Data extraction in duplicate was described in eight reviews.[38,41,44,46-49]. A list of excluded studies was provided by one SR.[43]

In twelve SRs, the included RCTs and the populations within were described in the text or an associated table of characteristics, however, the data reported were not comprehensive or sufficient.[38-44,46-50] In fact, the included trials were described in sufficient detail in one SR.[45] In seven SRs, the mutations within the populations were not described in detail[38,43,44,46,48-50].

The risk of bias was not assessed in all SRs and in several SRs the results from the assessment were not presented fulsomely or at all. None of the included SRs extracted or reported the information regarding the funding of the primary studies.[38-50]

In ten SRs, results were combined for meta-analysis using appropriate methods.[38,40-46,49,50] However, in one study, heterogeneity was not considered for pooling of results[40] and in two SRs, no clear justification was provided for the pooling of results.[47,48] The impact of any potential biases on the meta-analysis was not considered in ten SRs,[38-41,43-49] and the overall impact of any biases across the included trials was discussed in only two SRs.[42,43] The majority of the included SRs reported low or negligible heterogeneity related to the reported outcomes, and in those which did report significant heterogeneity, the potential causes were discussed.[38,39,41-46,48-50] Publication bias analysis was conducted, and its potential impact on the outcomes was discussed in six SRs.[40-42,44,46,50] In the remaining studies, either the publication bias analysis was not conducted, or its results or impact were not reported.[38,39,43,45,47-49] The potential conflicts of interest and sources of funding were declared in all but one SR.[38-46,48-50] AMSTAR 2 is not intended to comprehensively assess the quality of NMA so only the relevant SR features were assessed.

Table 10: Critical Appraisal of Included Systematic Reviews Using AMSTAR 2

Systematic Review	AMSTAR 2 – Item Number																Rating
	1	2[a]	3	4[a]	5	6	7[a]	8[a]	9[a]	10	11	12	13	14	15	16	
Wang, 2016[38]	Y	**N**	N	PY	N	Y	**N**	PY[b]	**N**	N	Y	N	N	Y	N	Y	**Critical**[c] (3 items)
Lee, 2017[39]	Y	**N**	N	PY	N	Y	**N**	PY	**N**	N	Y	N	N	Y	N	Y	**Critical**[c] (3 items)
Sheng, 2017[40]	Y	**N**	N	**N**	Y	N	**N**	PY	PY	N	N	N	N	N	Y	Y	**Critical**[c] (3 items)
Huang, 2018[41]	Y	**N**	N	PY	N	Y	**N**	PY	**N**	N	Y	N	N	Y	Y	Y	**Critical**[c] (3 items)
Jiang, 2018[42]	Y	**N**	N	PY	Y	N	**N**	PY	Y	N	Y	Y	Y	Y	Y	Y	**Critical**[c] (2 items)
Abdel-Rahman, 2018[43]	Y	**N**	N	**N**	N	N	Y	PY[b]	Y	N	Y	N	Y	Y	N	Y	**Critical**[c] (2 items)
Liu, 2018[44]	Y	**N**	N	PY	N	Y	**N**	PY[d]	Y	N	Y	N	N	Y	Y	Y	**Critical**[c] (2 items)
Khan, 2018[45 b]	Y	**N**	N	PY	Y	N	**N**	Y	Y	N	Y	N	N	Y	N	Y	**Critical**[c] (2 items)
Lee, 2018[46]	Y	**N**	N	PY	Y	Y	**N**	PY[b]	**N**	N	Y	N	N	Y	Y	Y	**Critical**[c] (3 items)
Almutairi, 2019 [47]	Y	**N**	N	**N**	Y	Y	**N**	PY	PY	N	N	N	N	N	N	N	**Critical**[c] (3 items)
Cavanna, 2019[48]	Y	**N**	N	PY	N	Y	**N**	PY[b]	**N**	N	N	N	N	Y	N	Y	**Critical**[c] (3 items)
Vickers, 2019[49]	Y	PY[b]	N	PY	Y	N	**N**	**N**[b]	**N**	N	Y	N	N	Y	N	Y	**Critical**[c] (3 items)
An, 2021[50]	Y	**N**	N	PY	N	Y	**N**	PY	Y	N	Y	Y	N	Y	Y	Y	**Critical**[c] (2 items)

Y = yes; N = no; PY = partial yes.

[a]Item designated as a potentially critical flaw.

[b]Mutations were not adequately described.

[c]SR was rated to be of critically low methodological quality due to more than one critical flaw and possibly other potential weaknesses. The SR should not be relied on to provide an accurate and comprehensive summary of the available studies.

[d]SR was registered in PROSPERO.

Three SRs involved a NMA.[38-46,48-50] The critical appraisal their SR methods using AMSTAR 2 was rated to be of critically low methodological quality due to more than one critical flaw and possibly other potential weaknesses. For a SR involving a NMA, the confidence of the results is dependent not only on the SR methods using AMSTAR 2, but also on whether the analytic complexities in estimating specific pairwise effects in the NMA were assessed. In particular, the assumptions of goodness of fit of the model, homogeneity and consistency. The summaries of these assessments are provided in Table 11. One SR never reported on assessing any of these assumptions.[38-46,48-50] A second SR, did not report on goodness of fit of the models, briefly reported on homogeneity and indicated that consistency could not be assessed because the evidence network did not have any closed loops which was needed for their of assessment of consistency.[38-46,48-50].The third SR conducted an in-depth evaluation of all three assumptions and reported specific statistics for each assumption by outcome.[38-46,48-50] Of the three SRs it provided the most robust assessment of the NMA assumptions. However, as for the AMSTAR 2 assessment of these three SRs, the assessment of the assumptions reported did not alter the conclusion that these SRs should not be relied on to provide an accurate and comprehensive summary of the available studies.

Table 11: Assessment of Critical Assumptions for Network Meta-Analysis

Systematic Review	Goodness of fit	Homogeneity	Consistency
Almutairi, 2019 [47]	NR	NR	NR
Cavanna, 2019[48]	NR	Assessed I^2	NC
Vickers, 2019[49]	Assessed deviance information criterion	Assessed I^2	Assessed node splitting

NR = nor reported; NC = not calculable

Discussion

Summary of Evidence

Main Take-Aways

Immune checkpoint inhibitor monotherapy does not offer any significant benefit for overall survival or progression-free survival when compared to chemotherapy with docetaxel in patients with non-small-cell lung cancer with epidermal growth factor receptor gene mutation.

Consensus on the efficacy of these drugs in non-small-cell lung cancer with other mutations such *ROS1*, *RET*, and *ALK* remains unknown.

The safety of ICIs in patients with any mutation remains unclear based on the evidence presented in the included systematic reviews.

The aim of this overview of SRs was twofold: to determine the efficacy of atezolizumab, nivolumab or pembrolizumab monotherapy in patients with advanced or metastatic NSCLC and actionable driver mutations who have been previously treated with platinum chemotherapy, and to establish whether use is safe for patients.

The project scope was informed by engaging with clinical experts and decision-makers to better understand the considerations for treatment with these ICI drugs and the potential health system impacts. A total of 13 publications met the final inclusion criteria and reported findings from included RCTs on the use of atezolizumab, nivolumab or pembrolizumab monotherapy or docetaxel. Of these, one review reported additional comparators and used a network meta-analysis model to estimate the indirect effects of nivolumab to pemetrexed and best supportive care. All included reviews considered RCTs which reported *EGFR*-positive patients. A small proportion of patients in some of the RCTs included by the SRs were *ALK*-positive, however no data for *ALK*-positive patients was reported. There were no SRs of RCTs that reported any patients with an *RET* or *ROS1* mutation. All RCTs of *EGFR* positive patients included in the SRs were published between 2015 and 2017. This is not surprising given the relatively stable treatment landscape over the time period covered by the reviews, but we cannot rule out that RCT data for this population or others of interest have been published since August 2020 (the date of the most recent SR search).

Efficacy outcomes were limited to overall survival and progression-free survival and none explicitly reported details of the interventions (e.g., dosing regimen, duration of treatment, dosing interval). There was little data to inform the interpretation of

the study results based on the context of the clinical trial. It would have been informative to consider how long patients were followed, what other anti-cancer treatments may have been administered and what the rates of patient treatment switching were. None of the review reported safety outcomes specific to patients with actionable driver mutations.

Patients in all studies were eligible to receive ICI drugs in the RCTs included in the reviews if they had a history of previous treatment but the reviews did not provide details about which medications were considered in the patients from the RCTs included. These details are likely reported in the eligibility criteria of the primary studies. No patient characteristics were reported for the individuals with *EGFR* gene mutations from the RCTs considered in the reviews, only characteristics for broader groups of NSCLC patients with and without actionable driver mutations were reported in four reviews. In these patients, mean age broadly ranged from age 60 years to 65 years and the proportion of male patients ranged from 47% to 85%. One review considered *EGFR*-positive patient histology (squamous versus non-squamous) combined with PD-L1 levels. A careful, comprehensive examination of patient characteristics in context with the study design is necessary to understand the extent to which the findings are limited by differences in the study populations (i.e., due to baseline patient characteristics). It is unclear whether patients in the included studies are likely to be broadly generalizable to the current Canadian setting.

The methodological quality of the SRs as assessed using AMSTAR2 varied, and appraisal was limited by insufficient reporting of many items and or lack of rationale to support decisions made at the review level. This made it difficult to assess the methodological rigor. At least half of the included reviews could be considered relatively poor quality as they did not report or address fundamental methodological components, including comprehensive details about the search strategy, the selection process and characteristics of the included RCTs and patients or did not assess risk of bias.

In six SRs that did assess risk of bias for the included RCTs, lack of blinding was an overall limitation. The SRs provided insufficient detail for the individual RCTs considered to permit sufficient understanding of how these biases could have impacted study findings, if at all.

Interpretation of Clinical Results

Benefits of ICI monotherapy in patients with NSCLC with actionable driver mutations

Based on the results of this overview, there is overall evidence that ICI monotherapy does not offer any significant benefit in improving OS and PFS over conventional chemotherapy when used for the treatment of NSCLC with *EGFR* mutation following another treatment, though there is insufficient evidence to evaluate or account for prior therapies.[38-50] While all of the reviews were assessed to have reporting limitations which may have influenced methodological quality, there is consistency of findings across the included reviews for overall survival.

In one NMA reporting a subgroup of patients with non-squamous NSCLC with *EGFR* mutation and PD-L1 expression levels of ≥ 5% may benefit from nivolumab monotherapy more than those with PD-L1 expression levels of <5%.[49] However, as this was a single review using an NMA approach, and the quantity of evidence available in the network was unclear, these results should be interpreted with caution. The RCTs included in the SRs were broadly assessed to be at low risk of bias for most domains, although lack of blinding was a limitation noted universally, so detection and performance bias cannot be ruled out. Although one SR did report the proportion of Asians and non-Asians included in their analyses,[49] the majority of the SRs included in this overview did not report the sex, age distribution, ethnicity or any other characteristics of patients with NSCLC with *EGFR* mutations making it difficult to assess how ICI monotherapy might perform across different demographic groups.[38-48,50] Data for other populations of interest were not reported, except to note that very small proportions of participants in the included trials (under 5%) had *ALK* mutations. None of the RCTs included in any of the SRs considered *ROS1* or *RET* mutations and so the efficacy of ICI drugs in these patient groups remains unclear.

Safety of ICI monotherapy in patients with NSCLC with actionable driver mutations

Adverse and severe adverse effects associated with atezolizumab, nivolumab and pembrolizumab were not assessed for the populations of *EGFR*-positive patients in the included SRs, and so no conclusions can be made regarding the safety of these ICI drugs in patients with NSCLC and *EGFR* gene mutations. Data for other populations of interest were not reported, except to note that small proportions of participants in the included trials (under 5%) had *ALK* mutations. None of the RCTs included in any of the SRs considered *ROS1* or *RET* gene mutations and so the efficacy of ICI drugs in these patients groups also remains unclear. Harms commonly documented with ICI drugs include fatigue, skin rash, diarrhea or constipation, nausea, vomiting, decreased appetite, cough, shortness of breath, fever, chills, body aches, joint or muscle pain, and changes in liver function.[55] Additionally, rare but serious side effects such as immune-related adverse events, including pneumonitis, colitis,

hepatitis, or thyroid disorders, may occur. Patients receiving ICI drug therapy require close monitoring by healthcare providers to detect and manage side effects promptly.[56]

Strengths and Limitations of the Overview

Strengths

We designed, implemented, and conducted an overview of SRs following the best practices outlined in the Cochrane Handbook of SRs of Interventions. The literature search was continuously updated to include the most recent reviews published up to 24th April, 2024. We located a number of reviews, each with varying scope and methodology, that broadly converged on similar conclusions which adds to the robustness of this overview of reviews.

Limitations

The main limitations of this review were the lack of identified clinical evidence for any *ALK*-, *RET*- or *ROS1*-positive patients, the methodological quality of the included SRs and the lack of clinical evidence to inform any conclusions about the safety for the interventions in any population of interest. Interpretation of the reported clinical evidence was limited by the reporting quality of the SRs. This overview did not capture RCTs published since the last search date of the included SRs (18 August 2020) and evidence from observational studies was not considered.[32] Only 2 clinical efficacy outcomes were reported. It is not clear if data for other outcomes of interest, including harms, may be available for patients with actionable driver mutations from the primary study publications or other published records. This overview relied on RCT data reported by the included SRs, which was insufficient to answer our research questions fulsomely. Data extracted from the SRs and the included RCTs were not cross-checked for accuracy or missing information against the primary study publications, except where discrepancies were found.

Conclusions and Implications for Policy-Making

Main Take-Aways

The findings suggest that immune checkpoint inhibitor monotherapy may not provide significant improvements in overall survival and progression-free survival compared to chemotherapy. However, histology and PD-L1 expression may help inform which non-small-cell lung cancer patient population could see a beneficial response. The safety profile of immune checkpoint inhibitors was not examined for specifically for patients with genetic mutations, making it challenging to determine their overall safety.

What is the evidence for the clinical efficacy of atezolizumab, nivolumab, and pembrolizumab monotherapy in previously treated patients with advanced or metastatic NSCLC with actionable driver mutations?

To determine the efficacy of use of atezolizumab, nivolumab, and pembrolizumab monotherapy in previously treated patients with advanced or metastatic NSCLC with actionable driver mutations, an overview of SRs was undertaken. Thirteen reviews were included in this review. We conclude based on efficacy data from up to 4 RCTs for overall survival and 2 RCTs for progression-free survival included in the SRs that as a class, ICI monotherapy does not provide significant improvements in OS and PFS relative to chemotherapy.

Findings from one systematic review suggest that histology and PD-L1 expression may be informative to the selection of patients who may see a beneficial response to ICI drugs. When histology is considered, in patients with squamous NSCLC and *EGFR* mutation, nivolumab may be more effective than docetaxel and pemetrexed, irrespective of PD-L1 expression level. However, there was no information presented to contextualize these findings alongside patient or trial characteristics. All of the SRs included in this overview did not provide information on the demographics or health status of patients with NSCLC and *EGFR* mutations, making it challenging to recommend ICI drugs in any age, sex or groups with NSCLC harbouring actionable mutations in Canada. PD-L1 expression and histology may be valuable indicators of potential response to ICI drugs in the second-line setting or beyond, however, no evidence for pembrolizumab or atezolizumab are available in the RCTs included by the SRs to consider consistency in the treatments available.

The results from all included SRs should be interpreted with caution due to significant methodological and reporting flaws. Additionally, the findings regarding clinical efficacy in populations with *EGFR* may not accurately and comprehensively represent the available RCTs.

What is the evidence for the safety of atezolizumab, nivolumab, and pembrolizumab monotherapy in previously treated patients with advanced or metastatic NSCLC with actionable driver mutations?

None of the included SRs in our overview of reviews specifically examined the relative adverse effects and safety profile of ICI monotherapies in patients with mutated non-small cell lung cancer (NSCLC). This is likely attributable to reporting limitations of the RCTs which did not stratify the reported safety data by mutation status. As a result, it is challenging to determine the overall safety of the individual ICI monotherapies or as a class in this patient population. There is no expectation that toxicity profile would differ for atezolizumab, nivolumab, and pembrolizumab and is reasonable to expect safety overall would be similar to first- and second-line use, and to unmutated tumours. SRs of higher quality, RCTs, or observational studies focusing on analyzing the safety of ICI monotherapy in mutated NSCLC patients, are needed to ascertain the overall safety of ICI monotherapy drugs in these patients.

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Authors

Clinical Review

George A. Wells acted as the principal investigator by developing and leading the approach, and contributed to validation of the results, interpretation of the results, drafting, and finalizing the report.

Shariq Najeeb contributed by screening studies; extracting data; analyzing and interpreting results, figures, and tables; verifying and assessing quality; and drafting and revising the report.

Said Yousef Abdelrazeq contributed by screening studies; extracting data; analyzing and interpreting results, figures, and tables; verifying and assessing quality; and drafting and revising the report.

Xiaoqin WANG contributing by screening of the studies; extracting data; and proof-reading; verifying and assessing quality.

Shannon Kelly contributed to the conceptualization and design of the approach, provided research oversight, and contributed to the interpretation of results and drafting and finalizing the report.

Nazmun Nahar contributed by drafting tables and assisting with referencing of the report.

Melissa Brouwers contributed to the conceptualization and design of the approach and provided final approval to the version of the report.

Research Information Science

Becky Skidmore designed and executed the literature search strategy, monitored search alerts, prepared the search methods section and appendix, and provided final approval to the version of the report.

Contributors

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Conflicts of Interest

No conflicts of interest were declared.

Appendix 1: Literature Search Strategy

NSCLC – Immunotherapy

Final Strategy

2024 Jan 26

Last Update: 2024 Apr 24

Ovid Multifile

Database: Embase Classic+Embase <1947 to 2024 April 23>, Ovid MEDLINE(R) ALL <1946 to April 23, 2024>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to April 17, 2024>

Search Strategy:

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1 Carcinoma, Non-Small-Cell Lung/ (154252)

2 (Squamous Cell Carcinoma/ or Adenocarcinoma/ or Large Cell Carcinoma/) and exp Lung Neoplasms/ (83483)

3 ((neoplas* or cancer* or tumo?r* or carcinoma* or malignan* or oncolog* or h?emangioma* or blastoma* or carcinosarcoma* or carcino-sarcoma* or leuk?emia* or lymphoma* or melanoma* or mesenchymoma* or sarcoma* or thymoma* or granuloma*) adj3 ((non-small-cell or nonsmall-cell or large-cell or squamous-cell or epidermoid* or planocellular or plano-cellular) adj3 (lung or lungs or pneumo* or bronch* or pulmon*or pleuropulmon* or pleuro-pulmon*))).tw,kw,kf. (255204)

4 ((adenocancer* or adenoma* or adenocarcinoma* or adeno-carcinoma*) adj3 (lung or lungs or pneumo* or bronch* or pulmon* or pleuropulmon* or pleuro-pulmon*)).tw,kw,kf. (89960)

5 (NSCLC or NSCLCs).tw,kw,kf. (183616)

6 or/1-5 [NSCLC] (409414)

7 exp Neoplasm Metastasis/ (1095139)

8 Neoplasm Recurrence, Local/ (198219)

9 (meta adj sta*).tw,kw,kf. (1751)

10 (metastas* or metastatic* or recur* or secondar* or relaps* or advanc* or inoperab* or disseminat* or spread or migration? or lethal* or incurable or noncurable or non-curable or uncurable or progressive or terminal or invasiv* or aggressiv*).tw,kw,kf. (12463012)

11 (late? adj2 stage?).tw,kw,kf. (188459)

12 ((stage? or grade? or type?) adj2 (3a* or 3b* or 3c* or III* or 4a* or 4b* or 4c* or IV*)).tw,kw,kf. (545350)

13 ("stage 3" or "stage 4" or met or mets or N1 or N2? or N3? or pN1? or pN2? or pN3?).tw,kw,kf. (1468368)

14 or/7-13 [ADVANCED/METASTATIC CANCER] (14133430)

15 6 and 14 [NSCLC - ADVANCED/METASTATIC] (254024)

16 (atezolizumab* or "mpdl 3280" or mpdl3280 or "mpdl 3280a" or mpdl3280a or "rg 7446" or rg744 or "ro 5541267" or ro5541267 or tecentriq$2 or tecntriq$2 or anti-PDL1 or anti-PD-L1 or 0INE2SFD9E or 52CMI0WC3Y or 1380723-44-3).tw,kw,kf,rn. (31709)

17 Nivolumab/ (47234)

18 (nivolumab* or "ba 1104" or ba1104 or "bms 936558" or bms936558 or "cmab 819" or cmab819 or HSDB 8256 or L01XC17 or "ly 01015" or ly01015 or "mdx 1106" or mdx1106 or "ono 4538" or ono4538 or opdivo$2 or "pbp 2101" or pbp2101 or xdivane$2 or 31YO63LBSN or 946414-94-4).tw,kw,kf,rn. (53862)

19 (pembrolizumab* or "bcd 201" or bcd201 or keytruda$2 or lambrolizumab$2 or "mk 3475" or mk3475 or "pbp 2102" or pbp2102 or "sch 900475" or sch900475 or xtrudane$2 or DPT0O3T46P or HSDB 8257 or L01XC18 or 1374853-91-4).tw,kw,kf. (31871)

20 Antineoplastic Agents, Immunological/ (15243)

21 ((antineoplastic? or anti-neoplastic?) adj2 (monoclonal antibod* or mono-clonal antibod* or monoclonal anti-bod* or mono-clonal anti-bod* or MAB or MABs)).tw,kw,kf. (62)

22 Immune Checkpoint Inhibitors/ (41206)

23 ((immune checkpoint or CTLA-4 or Cytotoxic T-Lymphocyte-Associated Protein 4 or PD-1 or PD-1-PD-L1 or PD-L1 or Programmed Cell Death Protein 1 or Programmed Death-Ligand 1) adj3 (inhibition or inhibitor? or blocker? or blockade?)).tw,kw,kf. (118479)

24 ((ICI or ICIs) adj5 immun*).tw,kw,kf. (30282)

25 or/16-24 [DRUGS OF INTEREST, DRUG CLASS] (186759)

26 15 and 25 [ADVANCED/METASTATIC NSCLC - DRUGS/DRUG CLASS OF INTEREST] (27135)

27 exp Animals/ not Humans/ (17781750)

28 26 not 27 [ANIMAL-ONLY REMOVED] (25777)

29 (address or autobiography or bibliography or biography or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt. (4742130)

30 28 not 29 [OPINION PIECES, PUBLICATION TYPES NOT OF INTEREST REMOVED] (25221)

31 Systematic Review.pt. (268117)

32 exp Systematic Reviews as Topic/ (47785)

33 Meta Analysis.pt. (199401)

34 exp Meta-Analysis as Topic/ (85250)

35 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw,kf. (715293)

36 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or evidence map* or meta-review* or meta-overview* or meta-synthes* or mapping review? or rapid review* or "review of reviews" or scoping review? or umbrella review? or technology assessment* or HTA or HTAs).tw,kw,kf. (926991)

37 exp Technology Assessment, Biomedical/ (30305)

38 (cochrane or health technology assessment or evidence report or systematic reviews).jw. (70476)

39 Network Meta-Analysis/ (14873)

40 (network adj (MA or MAs)).tw,kw,kf. (55)

41 (NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw,kf. (26556)

42 indirect* compar*.tw,kw,kf. (9267)

43 (indirect treatment* adj1 compar*).tw,kw,kf. (1864)

44 (mixed treatment* adj1 compar*).tw,kw,kf. (1601)

45 (multiple treatment* adj1 compar*).tw,kw,kf. (579)

46 (multi-treatment* adj1 compar*).tw,kw,kf. (16)

47 simultaneous* compar*.tw,kw,kf. (3087)

48 mixed comparison?.tw,kw,kf. (174)

49 or/31-48 [SR FILTER] (1411289)

50 30 and 49 [ADVANCED/METASTATIC NSCLC - DRUGS/DRUG CLASS OF INTEREST - SRs] (1716)

51 limit 50 to yr="2013-current" [DATE LIMIT APPLIED] (1706)

52 51 use medall [MEDLINE RECORDS] (558)

53 exp non small cell lung cancer/ (241315)

54 ((neoplas* or cancer* or tumo?r* or carcinoma* or malignan* or oncolog* or h?emangioma* or blastoma* or carcinosarcoma* or carcino-sarcoma* or leuk?emia* or lymphoma* or melanoma* or mesenchymoma* or sarcoma* or thymoma* or granuloma*) adj3 ((non-small-cell or nonsmall-cell or large-cell or squamous-cell or epidermoid* or planocellular or plano-cellular) adj3 (lung or lungs or pneumo* or bronch* or pulmon*or pleuropulmon* or pleuro-pulmon*))).tw,kw,kf. (255204)

55 ((adenocancer* or adenoma* or adenocarcinoma* or adeno-carcinoma*) adj3 (lung or lungs or pneumo* or bronch* or pulmon* or pleuropulmon* or pleuro-pulmon*)).tw,kw,kf. (89960)

56 (NSCLC or NSCLCs).tw,kw,kf. (183616)

57 or/53-56 [NSCLC] (390475)

58 exp lung metastasis/ (70505)

59 metastasis/ (495014)

60 micrometastasis/ (8423)

61 tumor recurrence/ (74982)

62 (meta adj sta*).tw,kw,kf. (1751)

63 (metastas* or metastatic* or recur* or secondar* or relaps* or advanc* or inoperab* or disseminat* or spread or migration? or lethal* or incurable or noncurable or non-curable or uncurable or progressive or terminal or invasiv* or aggressiv*).tw,kw,kf. (12463012)

64 (late? adj2 stage?).tw,kw,kf. (188459)

65 ((stage? or grade? or type?) adj2 (3a* or 3b* or 3c* or III* or 4a* or 4b* or 4c* or IV*)).tw,kw,kf. (545350)

66 ("stage 3" or "stage 4" or met or mets or N1 or N2? or N3? or pN1? or pN2? or pN3?).tw,kw,kf. (1468368)

67 or/58-66 [ADVANCED/METASTATIC CANCER] (14025151)

68 57 and 67 [NSCLC - ADVANCED/METASTATIC] (238266)

69 atezolizumab/ (17334)

70 (atezolizumab* or "mpdl 3280" or mpdl3280 or "mpdl 3280a" or mpdl3280a or "rg 7446" or rg744 or "ro 5541267" or ro5541267 or tecentriq$2 or tecntriq$2 or anti-PDL1 or anti-PD-L1 or 0INE2SFD9E or 52CMI0WC3Y or 1380723-44-3).tw,kw,kf,rn. (31709)

71 nivolumab/ (47234)

72 (nivolumab* or "ba 1104" or ba1104 or "bms 936558" or bms936558 or "cmab 819" or cmab819 or HSDB 8256 or L01XC17 or "ly 01015" or ly01015 or "mdx 1106" or mdx1106 or "ono 4538" or ono4538 or opdivo$2 or "pbp 2101" or pbp2101 or xdivane$2 or 31YO63LBSN or 946414-94-4).tw,kw,kf,rn. (53862)

73 pembrolizumab/ (41310)

74 (pembrolizumab* or "bcd 201" or bcd201 or keytruda$2 or lambrolizumab$2 or "mk 3475" or mk3475 or "pbp 2102" or pbp2102 or "sch 900475" or sch900475 or xtrudane$2 or DPT0O3T46P or HSDB 8257 or L01XC18 or 1374853-91-4).tw,kw,kf. (31871)

75 immunological antineoplastic agent/ (15243)

76 antineoplastic monoclonal antibody/ (3192)

77 ((antineoplastic? or anti-neoplastic?) adj2 (monoclonal antibod* or mono-clonal antibod* or monoclonal anti-bod* or mono-clonal anti-bod* or MAB or MABs)).tw,kw,kf. (62)

78 immune checkpoint inhibitor/ (41530)

79 ((immune checkpoint or CTLA-4 or Cytotoxic T-Lymphocyte-Associated Protein 4 or PD-1 or PD-1-PD-L1 or PD-L1 or Programmed Cell Death Protein 1 or Programmed Death-Ligand 1) adj3 (inhibition or inhibitor? or blocker? or blockade?)).tw,kw,kf. (118479)

80 ((ICI or ICIs) adj5 immun*).tw,kw,kf. (30282)

81 or/69-80 [DRUGS OF INTEREST, DRUG CLASS] (193071)

82 68 and 81 [ADVANCED/METASTATIC NSCLC - DRUGS/DRUG CLASS OF INTEREST] (27455)

83 (exp animal/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/) not (exp human/ or exp human experiment/) (13434292)

84 82 not 83 [ANIMAL-ONLY REMOVED] (27113)

85 editorial.pt. (1492539)

86 84 not 85 [OPINION PIECES, PUBLICATION TYPES NOT OF INTEREST REMOVED] (26912)

87 "systematic review"/ (722201)

88 "systematic review (topic)"/ (34669)

89 meta analysis/ (512787)

90 "meta analysis (topic)"/ (55639)

91 (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw,kf. (715293)

92 (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or evidence map* or meta-review* or meta-overview* or meta-synthes* or mapping review? or rapid review* or "review of reviews" or scoping review? or umbrella review? or technology assessment* or HTA or HTAs).tw,kw,kf. (926991)

93 exp biomedical technology assessment/ (30305)

94 (cochrane or health technology assessment or evidence report or systematic reviews).jw. (70476)

95 network meta-analysis/ (14873)

96 (network adj (MA or MAs)).tw,kw,kf. (55)

97 (NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw,kf. (26556)

98 indirect* compar*.tw,kw,kf. (9267)

99 (indirect treatment* adj1 compar*).tw,kw,kf. (1864)

100 (mixed treatment* adj1 compar*).tw,kw,kf. (1601)

101 (multiple treatment* adj1 compar*).tw,kw,kf. (579)

102 (multi-treatment* adj1 compar*).tw,kw,kf. (16)

103 simultaneous* compar*.tw,kw,kf. (3087)

104 mixed comparison?.tw,kw,kf. (174)

105 or/87-104 [SR FILTER] (1532431)

106 86 and 105 [ADVANCED/METASTATIC NSCLC - DRUGS/DRUG CLASS OF INTEREST - SRs] (2059)

107 conference abstract.pt. (5118750)

108 106 not 107 [CONFERENCE ABSTRACTS REMOVED] (1600)

109 limit 108 to yr="2013-current" [DATE LIMIT APPLIED] (1590)

110 109 use emczd [EMBASE RECORDS] (1026)

111 ((neoplas* or cancer* or tumo?r* or carcinoma* or malignan* or oncolog* or h?emangioma* or blastoma* or carcinosarcoma* or carcino-sarcoma* or leuk?emia* or lymphoma* or melanoma* or mesenchymoma* or sarcoma* or thymoma* or granuloma*) adj3 ((non-small-cell or nonsmall-cell or large-cell or squamous-cell or epidermoid* or planocellular or plano-cellular) adj3 (lung or lungs or pneumo* or bronch* or pulmon*or pleuropulmon* or pleuro-pulmon*))).ti,ab,kw. (249854)

112 ((adenocancer* or adenoma* or adenocarcinoma* or adeno-carcinoma*) adj3 (lung or lungs or pneumo* or bronch* or pulmon* or pleuropulmon* or pleuro-pulmon*)).ti,ab,kw. (88832)

113 (NSCLC or NSCLCs).ti,ab,kw. (182264)

114 or/111-113 [NSCLC] (343224)

115 (meta adj sta*).ti,ab,kw. (1731)

116 (metastas* or metastatic* or recur* or secondar* or relaps* or advanc* or inoperab* or disseminat* or spread or migration? or lethal* or incurable or noncurable or non-curable or uncurable or progressive or terminal or invasiv* or aggressiv*).ti,ab,kw. (12411069)

117 (late? adj2 stage?).ti,ab,kw. (187804)

118 ((stage? or grade? or type?) adj2 (3a* or 3b* or 3c* or III* or 4a* or 4b* or 4c* or IV*)).ti,ab,kw. (541727)

119 ("stage 3" or "stage 4" or met or mets or N1 or N2? or N3? or pN1? or pN2? or pN3?).ti,ab,kw. (1461134)

120 or/115-119 [ADVANCED/METASTATIC CANCER] (13874954)

121 114 and 120 [NSCLC - ADVANCED/METASTATIC] (216389)

122 (atezolizumab* or "mpdl 3280" or mpdl3280 or "mpdl 3280a" or mpdl3280a or "rg 7446" or rg744 or "ro 5541267" or ro5541267 or tecentriq$2 or tecntriq$2 or anti-PDL1 or anti-PD-L1 or 0INE2SFD9E or 52CMI0WC3Y or 1380723-44-3).ti,ab,kw. (20925)

123 (nivolumab* or "ba 1104" or ba1104 or "bms 936558" or bms936558 or "cmab 819" or cmab819 or HSDB 8256 or L01XC17 or "ly 01015" or ly01015 or "mdx 1106" or mdx1106 or "ono 4538" or ono4538 or opdivo$2 or "pbp 2101" or pbp2101 or xdivane$2 or 31YO63LBSN or 946414-94-4).ti,ab,kw. (31806)

124 (pembrolizumab* or "bcd 201" or bcd201 or keytruda$2 or lambrolizumab$2 or "mk 3475" or mk3475 or "pbp 2102" or pbp2102 or "sch 900475" or sch900475 or xtrudane$2 or DPT0O3T46P or HSDB 8257 or L01XC18 or 1374853-91-4).ti,ab,kw. (30734)

125 ((antineoplastic? or anti-neoplastic?) adj2 (monoclonal antibod* or mono-clonal antibod* or monoclonal anti-bod* or mono-clonal anti-bod* or MAB or MABs)).ti,ab,kw. (60)

126 ((immune checkpoint or CTLA-4 or Cytotoxic T-Lymphocyte-Associated Protein 4 or PD-1 or PD-1-PD-L1 or PD-L1 or Programmed Cell Death Protein 1 or Programmed Death-Ligand 1) adj3 (inhibition or inhibitor? or blocker? or blockade?)).ti,ab,kw. (112818)

127 ((ICI or ICIs) adj5 immun*).ti,ab,kw. (29826)

128 or/122-127 [DRUGS OF INTEREST, DRUG CLASS] (152247)

129 121 and 128 [ADVANCED/METASTATIC NSCLC - DRUGS/DRUG CLASS OF INTEREST] (21726)

130 limit 129 to yr="2013-current" (21693)

131 130 use coch [CDSR RECORDS] (3)

132 52 or 110 or 131 [ALL DATABASES] (1587)

133 (2024012* or 2024013* or 202402* or 202403* or 202404*).dt. (416908)

134 52 and 133 [MEDLINE RECORDS - UPDATE PERIOD] (29)

135 (2024012* or 2024013* or 202402* or 202403* or 202404*).dc. (643921)

136 110 and 135 [EMBASE RECORDS - UPDATE PERIOD] (51)

137 (2024012* or 2024013* or 202402* or 202403* or 202404*).up. (1640026)

138 131 and 137 [CDSR RECORDS - UPDATE PERIOD] (0)

139 134 or 136 or 138 [ALL DATABASES - UPDATE PERIOD] (80)

140 remove duplicates from 139 (55) [TOTAL UNIQUE RECORDS – UPDATE PERIOD]

141 140 use medall [MEDLINE UNIQUE RECORDS - UPDATE PERIOD] (28)

142 140 use emczd [EMBASE UNIQUE RECORDS - UPDATE PERIOD] (27)

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Appendix 2: Assessment of Included Study Overlap Across Included Systematic Reviews

Table 12. General characteristics of primary studies as reported in the included systematic reviews.

Characteristics[a]	Randomized Controlled Trial (author and trial name)			
	Borghaei et al. (CHECKMATE-057)	Herbst et al. (KEYNOTE-010)	Rittmeyer at al. (OAK)	Fehrenbacher et al. (POPLAR)
Clinical trial no.	NCT01673867	NCT01905657	NCT02008227	NCT01903993
Total number of patients analyzed (N)	582	1,034	850	287
Included mutations of interest	*EGFR*, *ALK*[b]	*EGFR, ALK*[b]	*EGFR, ALK*[b]	*EGFR,* ALK[b]
Intervention (n)	Nivolumab (292)	Pembrolizumab (691)	Atezolizumab (425)	Atezolizumab (144)
Comparator (n)	Docetaxel (290)	Docetaxel (343)	Docetaxel (425)	Docetaxel (143)
Outcomes of interest assessed for population with relevant mutation[b]	OS, PFS	OS, PFS	OS	OS
Overall findings in population of interest[c]	No significant difference in OS and PFS between intervention and comparator in patients with NSCLC with *EGFR* mutation.	No significant difference in OS and PFS between intervention and comparator in patients with NSCLC with *EGFR* mutation.	No significant difference in OS between intervention and comparator in patients with NSCLC with *EGFR* mutation. PFS not reported.	No significant difference in OS between intervention and comparator in patients with NSCLC with *EGFR* mutation. PFS not reported.

ALK = Anaplastic Lymphoma Kinase; *EGFR* = Epidermal Growth Factor Receptor; OS = overall survival, PFS = Progression-free survival.

[a] This table was adapted from data shared in two included SRs[47,50].

[b] Patients with these mutations were documented in the study population, however, outcomes were only reported for *EGFR*-positive patients.

[c] All findings are based on results reported for EGFR-positive patients.

Table 13: Overlap of RCTs in the Systematic Reviews – Overall Survival

Systematic Review (author, year)	Number of RCTs Included in the SRs that Report the Outcome in Population of Interest	RCTs Included in the Systematic Review (author, study)			
		Borghaei et al. CHECKMATE-057	Herbst et al. KEYNOTE-010	Rittmeyer at al. OAK	Fehrenbacher et al. POPLAR
Wang, 2016[38]	2	x	x	NI	NI
Lee, 2017[39]	3	x	x	NI	x
Sheng, 2017[40]	2	x	x	NI	NI
Huang, 2018[41]	4	x	x	x	x
Jiang, 2018[42]	3	x	x	x	NI
Abdel-Rahman, 2018[43]	4	x	x	x	x
Liu, 2018[44]	3	x	x	x	NI
Khan, 2018[45]	3	Unspecified			
Lee, 2018[46]	4	x	NI	x	x
Almutairi, 2019[47]	4[a]	Unspecified			
Cavanna, 2019[48]	4[a]	x	x	x	x
Vickers, 2019[49]	(31)[b]	Unspecified			
An, 2021[50]	3	x	x	x	NI
Number of times studies cited in overlaps[c]		10	9	7	5

NI = not included; NR = not reported; RCTs = randomized controlled trials.

[a]RCTs considered in the evidence network for the NMA.

[b]31 RCTs identified in the overall evidence network for the NMA but unspecified RCTs identified for the subgroup analysis for *EGFR* positive.

[c]The unspecified RCTs in three SRs are not included in the overall overlap.

Table 14: Overlap of RCTs in the Systematic Reviews – Progression Free Survival

Systematic Review (author, year)	Number of RCTs Included in the SRs that Report the Outcome in Population of Interest	RCTs Included in the Systematic Review (author, study)			
		Borghaei et al. CHECKMATE-057	Herbst et al. KEYNOTE-010	Rittmeyer at al. OAK	Fehrenbacher et al. POPLAR
Wang, 2016[38]	NI	NI	NI	NI	NI
Lee, 2017[39]	NI	NI	NI	NI	NI
Sheng, 2017[40]	2	x	x	NI	NI
Huang, 2018[41]	NI	NI	NI	NI	NI
Jiang, 2018[42]	2	x	x	NI	NI
Abdel-Rahman, 2018[43]	NI	NI	NI	NI	NI
Liu, 2018[44]	NI	NI	NI	NI	NI
Khan, 2018[45]	2	Unspecified		NI	NI
Lee, 2018[46]	NI	NI	NI	NI	NI
Almutairi, 2019[47]	2[a]	Unspecified		NI	NI
Cavanna, 2019[48]	NI	NI	NI	NI	NI
Vickers, 2019[49]	(31)[b]	Unspecified		NI	NI
An, 2021[50]	2	x	x	NI	NI
Number of times studies cited in overlaps[c]		3	3	0	0

NI = not included; NR = not reported; RCTs = randomized controlled trials.

[a]RCTs considered in the evidence network for the NMA.

[b]31 RCTs identified in the overall evidence network for the NMA but unspecified RCTs identified for the subgroup analysis for *EGFR* positive.

[c]The unspecified RCTs in three SRs are not included in the overall overlap.

Appendix 3: Characteristics of the Included Systematic Reviews

Table 15: Search Databases, Inclusion and Exclusion Criteria, Mutation and PD-L1 Levels, Conclusion, and Funding Source of the Included Studies

First author, publication year	Search databases *Date of Search* Publication years of included primary studies	Inclusion criteria	Mutation, PD-L1 levels	Exclusion criteria	Funding source	Authors' conclusion
Wang, 2016[38]	ScienceDirect, and Web of Science. *20 May 2016* 2015 to 2016	Studies evaluated anti-PD-1/PD-L1 agents for NSCLC patients with or without a report of PD-L1 expression level. Studies included 1 or all the following: ORR, OS, and PFS.	*EGFR* Positive NR	Letters, editorials, expert opinions, case reports, duplicate publications, and reviews.	None	The results showed a significant improvement in OS of patients with wild-type *EGFR*; nevertheless, the same results were not observed in patients with mutant *EGFR*
Lee, 2017[39]	MEDLINE, EMBASE, PubMed, and the Cochrane Central Register of Controlled Trials databases *01 Jan.1996 to 01 July 2016* 2015 to 2016	Randomized trials that compared immune checkpoint inhibitors against chemotherapy in the second-line setting.	*EGFR* Positive NR	NR	None	In *EGFR*-mutant advanced NSCLC, immune checkpoint inhibitors do not improve OS over that with docetaxel.
Sheng, 2017[40]	Cochrane Controlled Trial Register, Embase, Medline, Science Citation Index *NR* 2015 to 2016	RCTs met the following criteria: (1) They dealt only with previously treated advanced NSCLC patients. (2) They enrolled patients treated with anti-PD-1/PD-L1 therapy or *EGFR*TKIs.(3) Acceptable	*EGFR* Positive NR	NR	None	The HRs in this analysis of OS favored anti-PD-1/PD-L1 therapy across most prespecified subpopulation; the exceptions were the subpopulation who lived in the rest-of-the world geographic

First author, publication year	Search databases *Date of Search* Publication years of included primary studies	Inclusion criteria	Mutation, PD-L1 levels	Exclusion criteria	Funding source	Authors' conclusion
		comparator was docetaxel. (4) They could provide data about AE, RR, OS and PFS. (5) These studies are prospective.				region, those with age more than 75 years, those with central nervous system metastases, those who had never smoked, and those with *EGFR* mutation.
Huang, 2018[41]	PubMed, Web of Knowledge and Central databases *31 December 2016* 2015 to 2017	All eligible studies were randomized trials that compared the survival of anti-PD-1/PD-L1 immunotherapy against chemotherapy in adult patients with advanced NSCLC.	*EGFR* Positive NR	NR	NIHR Imperial Biomedical Research Centre, NIHR and Action Against Cancer.	'Patients with a … *EGFR* wild-type tumor have improved survival benefit from immunotherapy compared with … *EGFR* mutant NSCLC, respectively.'
Jiang, 2018[42]	PubMed, EMBASE and Cochrane Library *01 April 2017* 2015 to 2017	The inclusion criteria were: (1) randomized controlled trial; (2) patients with advanced or metastatic NSCLC after failure of previous treatments; (3) anti- PD-1/PD-L1 antibodies treatment as compared with chemotherapy; (4) published in English; (5) reported OR rate, toxicity	*EGFR* Positive NR	NR	Funding: Grants from the General Research Program of Zhejiang Provincial Department of Health	For patients with *EGFR* mutation, anti-PD-1/PD-L1 therapy was an unfavorable factor of PFS.

First author, publication year	Search databases *Date of Search* Publication years of included primary studies	Inclusion criteria	Mutation, PD-L1 levels	Exclusion criteria	Funding source	Authors' conclusion
		data, or at least one form of survival data.				
Abdel-Rahman, 2018[43] [d]	PubMed *01 February 2017* 2015 to 2017	Patients with histologically diagnosed pretreated advanced NSCLC. Interventions: The three PD-1/PD-L1 inhibitors (nivolumab, pembrolizumab and atezolizumab) vs docetaxel. Outcomes: Impact of different clinical/biological factors [including histology, age, smoking, ECOG PS, CNS metastasis, PD-L1 status, *EGFR* status, KRAS status and *ALK* status in prediction of outcomes of pretreated advanced NSCLC patients treated with PD-1/PDL1 inhibitors.	*EGFR* Positive NR	NR	None	No conclusion on mutation of interest.
Liu, 2018[44]	PubMed, Embase, and the Cochrane Library	RCTs, a comparison with docetaxel, at least one efficacy	*EGFR* Positive NR	Letters, expert opinions, case reports, reviews,	Major Project of Jiangxi Natural Science	NSCLC patients with wild-type *EGFR* or smoking

First author, publication year	Search databases *Date of Search* Publication years of included primary studies	Inclusion criteria	Mutation, PD-L1 levels	Exclusion criteria	Funding source	Authors' conclusion
	27 December 2017 2015 to 2017	outcome and one safety outcome reported, and the full text being available.		articles without available data, and duplicate publications.	Foundation, and the National Natural Science Foundation of China	history showed improved OS in the PD1/PDL1 group compared to that of the control group receiving docetaxel monotherapy; however, no such effect was seen for patients with *EGFR* mutation and a no-smoking history.
Khan, 2018[45 d]	PubMed, Cochrane Library, and Web of Science *01 December 2017* 2015 to 2017	RCTs comparing the anti-PD1/PD-L1 therapies with chemotherapy in advanced NSCLC. Also provided data of OS, PFS, and adverse events in order to analyze the efficacy and safety of IOs.	*EGFR* Positive NR	Any RCT with incomplete data was excluded.	National Natural Science Foundation Of China and Guangzhou Key Medical Discipline Construction Project	No conclusion on mutation of interest.
Lee, 2018[46]	MEDLINE, Embase, PubMed, and theCochrane Central Register of Controlled Trials. For abstracts-American Society of Clinical Oncology, the European Society	RCTs that compared IOs with docetaxel in the second-line setting compared to docetaxel to assess OS.	*EGFR* Positive NR	NR	None	Checkpoint inhibitors, compared with docetaxel, are associated with significantly prolong overall survival in second-line therapy in NSCLC. The finding of no

First author, publication year	Search databases *Date of Search* Publication years of included primary studies	Inclusion criteria	Mutation, PD-L1 levels	Exclusion criteria	Funding source	Authors' conclusion
	for Medical Oncology, and the World Conference on Lung Cancer. *30 January 2017* 2015 to 2017					overall survival benefit for patients with *EGFR* mutant tumors suggests that checkpoint inhibitors should be considered only after other effective therapies have been exhausted.
Almutairi, 2019 [47]	Medline/PubMed, Cochrane Library, and Embase, US FDA websites and the European Medicines Agency. *01 June 2018* NR	Phase II/III RCTs that assessed the efficacy and/or safety of FDA-approved IOs that target PD-1 (nivolumab, pembrolizumab) and its ligand PD-L1 (atezolizumab) in previously treated advanced NSCLC, including updates for these trials.	*EGFR* Positive NR	Studies on pediatric populations or comparing alternate treatment doses of the same product.	None	No clear conclusion on mutation of interest.
Cavanna, 2019[48]	MEDLINE, PubMed, clinicaltrials.gov, American Society of Clinical Oncology *NR* 2015 to 2017	Phase II and III RCTs of different second- and third-line IOs for NSCLC previously treated with TKIs, with available *EGFR* mutations.	*EGFR* Positive NR	NR	NR	Results suggest that patients with NSCLC and *EGFR* mutation, previously treated with TKIs, show better OS when treated

First author, publication year	Search databases *Date of Search* Publication years of included primary studies	Inclusion criteria	Mutation, PD-L1 levels	Exclusion criteria	Funding source	Authors' conclusion
						with docetaxel in comparison to checkpoint inhibitors treatment
Vickers, 2019[49]	MEDLINE, PubMed, EMBASE, Biosciences Information Service, Cochrane Library, Abstracts - scientific meetings, American Society of Clinical Oncology, the European Society of Medical Oncology, International Association for the Study of Lung Cancer. *01 September 2015* NR	Phase 2/3 RCTs in adult patients with locally advanced or metastatic NSCLC and whose disease had progressed after first-line chemotherapy. Intervention of interest (nivolumab pembrolizumab). Comparator of interest (docetaxel, and Best supportive care).	*EGFR* Positive PD-L1 < 5%; PD-L1 ≥ 5%	NR	Eli Lilly and Company	No clear conclusion on mutation of interest.
An, 2021[50]	PubMed, Embase, Cochrane Library, clinicaltrial.gov, China National Knowledge Infrastructure, WanFang database, VIP database (China Science and Technology	(1) Prospective RCTs; (2) evaluate the clinical efficacy of anti-PD-1/PD-L1 immunotherapy and chemotherapy in patients with NSCLC; (3) the study must report the OS,	*EGFR* Positive NR	(1) Retrospective or prospective observational cohort studies; (2) phase I trials; (3) reviews, meta analysis, letters, case reports,	Zhejiang Medical Health Science and Technology Planning Project.	*EGFR* might be a potential predictor for the therapeutic effect of anti PD-1/PD-L1 immunotherapy in specific patients with NSCLC.

First author, publication year	Search databases *Date of Search* Publication years of included primary studies	Inclusion criteria	Mutation, PD-L1 levels	Exclusion criteria	Funding source	Authors' conclusion
	Journal Database) and China Biology Medicine disc), *18 August 2020* 2015 to 2017	PFS, ORR and AEs (4) the HRs and risk ratios (RRs) with 95% CIs for OS and PFS and data including age, sex, histology, smoking status, PD-L1 expressing status, ECOG PS, *EGFR* and KRAS mutation status can be drawn out from the text.		conference abstracts, expert opinions, cell and animal experiments; (4) duplicate publications; (5) studies with insufficient data; (6) patients have inconsistent baselines.		

AE = adverse event; CNS = central nervous system; Chemo =chemotherapy; CNKI = China National Knowledge Infrastructure; ECOG PS = eastern cooperative oncology group performance score; *EGFR* = epidermal growth factor receptor ; FDA = food and drug administration; HRs = hazard ratios; KRAS = Kirsten rat sarcoma; MA = meta-analysis; RCTs = randomized control trials; OS = overall survival; NA = not available; NIHR = National Institutes of Health Research; NR = not reported; ORR = objective response rate; PFS = progression-free survival; QA = quality appraisal; RR = response rate; RRs = risk ratios; SR = systematic review; vs = versus.

Appendix 4: Excluded Records

Table 16: List of excluded studies with reason for exclusion

Number	Citation
No mutation of interest (n = 30)	
1.	Olivares-Hernandez, Alejandro, Gonzalez Del Portillo, Elisabet, Tamayo-Velasco, Alvaro, Figuero-Perez, Luis, Zhilina-Zhilina, Svetlana, Fonseca-Sanchez, Emilio, Miramontes-Gonzalez, Jose Pablo. Immune checkpoint inhibitors in non-small cell lung cancer: from current perspectives to future treatments-a systematic review. Annals of translational medicine. 2023. 11:354
2.	Chen, Mo, Wei, Lingyun, Wang, Qin, Xie, Jingyuan, Xu, Ke, Lv, Tangfeng, Song, Yong, Zhan, Ping. Efficacy of different therapies for brain metastases of non-small cell lung cancer: a systematic review and meta-analysis. Translational lung cancer research. 2023. 12:689-706
3.	Wu, Changjin, Li, Wentan, Tao, Hongyu, Zhang, Xiyan, Xin, Yu, Song, Ruomeng, Wang, Kaige, Zuo, Ling, Cai, Yuanyi, Wu, Huazhang, Hui, Wen. Cost-effectiveness of first-line immunotherapy for advanced non-small cell lung cancer with different PD-L1 expression levels: A comprehensive overview. Critical reviews in oncology/hematology. 2024. 193:104195
4.	Shimizu, Takashi, Inoue, Eisuke, Ohkuma, Ryotaro, Kobayashi, Shinichi, Tsunoda, Takuya, Wada, Satoshi. Soluble PD-L1 changes in advanced non-small cell lung cancer patients treated with PD-1 inhibitors: an individual patient data meta-analysis. Frontiers in immunology. 2023. 14:1308381
5.	Nuccio, Antonio, Viscardi, Giuseppe, Salomone, Fabio, Servetto, Alberto, Venanzi, Francesco Maria, Riva, Silvia Teresa, Oresti, Sara, Ogliari, Francesca Rita, Vigano, Mariagrazia, Bulotta, Alessandra, Cameron, Robert, Esposito, Alessandra, Hines, Jacobi, Bianco, Roberto, Reni, Michele, Cascone, Tina, Garassino, Marina Chiara, Torri, Valter, Veronesi, Giulia, Cinquini, Michela, Ferrara, Roberto. Systematic review and meta-analysis of immune checkpoint inhibitors as single agent or in combination with chemotherapy in early-stage non-small cell lung cancer: Impact of clinicopathological factors and indirect comparison between treatment strategies. European journal of cancer (Oxford, England : 1990). 2023. 195:113404
6.	Chen, Wei, Chen, Jiayi, Zhang, Lin, Cheng, Sheng, Yu, Junxian. Network meta-analysis of first-line immune checkpoint inhibitor therapy in advanced non-squamous non-small cell lung cancer patients with PD-L1 expression >= 50. BMC cancer. 2023. 23:791
7.	Hu, Yue, Liu, Shan, Wang, Lixing, Liu, Yu, Zhang, Duohan, Zhao, Yinlong. Treatment-free survival after discontinuation of immune checkpoint inhibitors in mNSCLC: a systematic review and meta-analysis. Frontiers in immunology. 2023. 14:1202822
8.	Li, Yan, Liang, Xueyan, Li, Huijuan, Chen, Xiaoyu. Efficacy and safety of immune checkpoint inhibitors for advanced non-small cell lung cancer with or without PD-L1 selection: A systematic review and network meta-analysis. Chinese medical journal. 2023. 136:2156-2165
9.	Xu, Z., Liang, J., Fu, R., Yang, L., Xin Chen, Y., Ren, W., Lu, Y., Qiu, X., Gu, Q.. Effect of PD-L1 Expression for the PD-1/L1 Inhibitors on Non-small Cell Lung Cancer: A Meta-analysis Based on Randomised Controlled Trials. Clinical oncology (Royal College of Radiologists (Great Britain)). 2023. 35:640-651
10.	Zhang, Chengkai, Zhou, Wenjianlong, Zhang, Dainan, Ma, Shunchang, Wang, Xi, Jia, Wang, Guan, Xiudong, Qian, Ke. Treatments for brain metastases from *EGFR*/*ALK*-negative/unselected NSCLC: A network meta-analysis. Open medicine (Warsaw, Poland). 2023. 18:20220574
11.	Yang, Fang, Wang, Yucai, Tang, Lin, Mansfield, Aaron Scott, Adjei, Alex A., Leventakos, Konstantinos, Duma, Narjust, Wei, Jia, Wang, Lifeng, Liu, Baorui, Molina, Julian R.. Efficacy of immune checkpoint inhibitors in non-small cell lung cancer: A systematic review and meta-analysis. Frontiers in oncology. 2022. 12:955440
12.	Kim, Jinchul, Ha, Hyerim, Park, Jisun, Cho, Jinhyun, Lim, Joo Han, Lee, Moon Hee. Association of Smoking Status with Efficacy of First-line Immune Checkpoint Inhibitors in Advanced Non-small Cell Lung Cancers: A Systematic Review and Meta-analysis. Journal of Cancer. 2022. 13:364-372

Number	Citation
13.	Peng, Siyu, Ying, Ariel Fangting, Tai, Bee Choo, Soo, Ross Andrew. A meta-analysis on immune checkpoint inhibitor efficacy for advanced non-small cell lung cancer between East Asians versus non-East Asians. Translational lung cancer research. 2020. 9:1124-1137
14.	Landre, Thierry, Justeau, Gregoire, Assie, Jean-Baptiste, Chouahnia, Kader, Davoine, Claire, Taleb, Cherifa, Chouaid, Christos, Duchemann, Boris. Anti-PD-(L)1 for KRAS-mutant advanced non-small-cell lung cancers: a meta-analysis of randomized-controlled trials. Cancer immunology, immunotherapy: CII. 2022. 71:719-726
15.	Di Federico, Alessandro, De Giglio, Andrea, Nuvola, Giacomo, Deiana, Chiara, Conci, Nicole, Gelsomino, Francesco, Ardizzoni, Andrea. PD-(L)1 inhibitors as single-agent or in combination with chemotherapy for advanced, PD-L1-high non-small cell lung cancer: a meta-analysis. Future oncology (London, England). 2021. 17:4415-4424
16.	Zheng, Yuhui, Yao, Meihong, Yang, Yinghong. Higher Tumor Mutation Burden Was a Predictor for Better Outcome for NSCLC Patients Treated with PD-1 Antibodies: A Systematic Review and Meta-analysis. SLAS technology. 2021. 26:605-614
17.	Hu, Caihong, Liang, Zhengbo, Lai, Ping, Wang, Xiaofang, Zhao, Changming. Efficacy of atezolizumab to treat non-small-cell lung cancer: a meta-analysis based on randomized clinical trials. Die Pharmazie. 2021. 76:215-219
18.	Nan, Zhang, Guoqing, Wang, Xiaoxu, Yu, Yin, Mi, Xin, He, Xue, Li, Rong, Wang. The Predictive Efficacy of Tumor Mutation Burden (TMB) on Nonsmall Cell Lung Cancer Treated by Immune Checkpoint Inhibitors: A Systematic Review and Meta-Analysis. BioMed research international. 2021. 2021:1780860
19.	Connock, Martin, Armoiry, Xavier, Tsertsvadze, Alexander, Melendez-Torres, G. J., Royle, Pamela, Andronis, Lazaros, Clarke, Aileen. Comparative survival benefit of currently licensed second or third line treatments for epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (ALK) negative advanced or metastatic non-small cell lung cancer: a systematic review and secondary analysis of trials. BMC cancer. 2019. 19:392
20.	Silvinato, Antonio, Floriano, Idevaldo, Bernardo, Wanderley Marques. Advanced non-small cell lung cancer - Treatment with Pembrolizumab. Revista da Associacao Medica Brasileira (1992). 2019. 65:1423-1432
21.	Armoiry, Xavier, Tsertsvadze, Alexander, Connock, Martin, Royle, Pamela, Melendez-Torres, G. J., Souquet, Pierre-Jean, Clarke, Aileen. Comparative efficacy and safety of licensed treatments for previously treated non-small cell lung cancer: A systematic review and network meta-analysis. PloS one. 2018. 13:e0199575
22.	Crequit, Perrine, Chaimani, Anna, Yavchitz, Amelie, Attiche, Nassima, Cadranel, Jacques, Trinquart, Ludovic, Ravaud, Philippe. Comparative efficacy and safety of second-line treatments for advanced non-small cell lung cancer with wild-type or unknown status for epidermal growth factor receptor: a systematic review and network meta-analysis. BMC medicine. 2017. 15:193
23.	Kim, Jung Han, Kim, Hyeong Su, Kim, Bum Jun. Prognostic value of KRAS mutation in advanced non-small-cell lung cancer treated with immune checkpoint inhibitors: A meta-analysis and review. Oncotarget. 2017. 8:48248-48252
24.	Li, Jie, He, Qi, Yu, Xiu, Khan, Khalid, Weng, Xuanwen, Guan, Minjie. Complete response associated with immune checkpoint inhibitors in advanced non-small-cell lung cancer: a meta-analysis of nine randomized controlled trials. Cancer management and research. 2019. 11:1623-1629
25.	Chen, Shuo, Hu, Bin, Li, Hui. A meta-analysis of nivolumab for the treatment of advanced non-small-cell lung cancer. OncoTargets and therapy. 2018. 11:7691-7697
26.	Wu, Di, Duan, Chongyang, Wu, Fenfang, Chen, Liyong, Chen, Size. Which treatment is preferred for advanced non-small-cell lung cancer with wild-type epidermal growth factor receptor in second-line therapy? A meta-analysis comparing immune checkpoint inhibitor, tyrosine kinase inhibitor and chemotherapy. Oncotarget. 2017. 8:66491-66503
27.	Huang, Jiaxing, Zhang, Yaxiong, Sheng, Jin, Zhang, Hongyu, Fang, Wenfeng, Zhan, Jianhua, Zhou, Ting, Chen, Ying, Liu, Lin, Zhang, Li. The efficacy and safety of nivolumab in previously treated advanced non-small-cell lung cancer: a meta-analysis of prospective clinical trials. OncoTargets and therapy. 2016. 9:5867-5874

Number	Citation
28.	Chen, L., Zhao, P., Cao, K., Jin, L., Xu, R., Tang, X.. Efficacy and safety of immune checkpoint inhibitors in the treatment of non-small cell lung cancer: A meta-analysis. Journal of Mind and Behavior. 2018. 38:780-791
29.	Wan, Q., Yang, Y., Li, Y. L.. Efficacy and safety of PD-1 antibody/PD-L1 antibody versus docetaxel in non-small-cell lung cancer: a Meta-analysis. Chinese Journal of New Drugs. 2018. 27:229-235
30.	Zhang, Tongtong, Li, Shuluan, Chang, Jianhua, Qin, Yan, Li, Chao. Impact of BMI on the survival outcomes of non-small cell lung cancer patients treated with immune checkpoint inhibitors: a meta-analysis. *BMC cancer.* 2023. 23:1023
Ineligible outcome (n = 1)	
31.	Yu, Dahui, Yuan, Chong, Zhang, Hedan, Chu, Wenyan. The association of efficacy with PD-1/PD-L1 inhibition and tumor mutational burden in advanced nonsmall cell lung cancer: A PRISMA-guided literature review and meta-analysis. *Medicine.* 2022. 101:e29676
Ineligible intervention(s) (n = 8)	
32.	Wang, Zhen, Zhou, Fang, Xu, Shan, Wang, Kang, Ding, Huan. The efficacy and safety of immune checkpoint inhibitors for patients with *EGFR*-mutated non-small cell lung cancer who progressed on *EGFR* tyrosine-kinase inhibitor therapy: A systematic review and network meta-analysis. *Cancer medicine.* 2023. 12:18516-18530
33.	Daei Sorkhabi, Amin, ZareDini, Mahta, Fazlollahi, Asra, Sarkesh, Aila, Naseri, Amirreza, Mousavi, Seyed Ehsan, Nejadghaderi, Seyed Aria, Sullman, Mark J. M., Kolahi, Ali-Asghar, Safiri, Saeid. The safety and efficacy of tislelizumab, alone or in combination with chemotherapy, for the treatment of non-small cell lung cancer: a systematic review of clinical trials. *BMC pulmonary medicine.* 2023. 23:495
34.	Luciani, Andrea, Ghidini, Antonio, Borgonovo, Karen, Parati, Maria Chiara, Petrelli, Fausto. Outcome of non-small-cell lung cancer with driven mutations treated with anti-PD-(L)1 agents: A systematic review. *Tumori.* 2023. 109:442-449
35.	Chen, Jiarui, Liu, Xingyu, Zhang, Junhong, Huang, Zhao, Zeng, Wei, Hu, Jing, Chen, Gang, Gong, Yan, Liu, Yu, Xie, Conghua. Frontline anti-PD-1/PD-L1 versus bevacizumab in advanced non-small-cell lung cancer: a network meta-analysis. *Future oncology (London, England).* 2022. 18:1651-1664
36.	Ba, He, Liu, Lei, Peng, Qiang, Chen, Jie, Zhu, Yao-Dong. The relationship between blood-based tumor mutation burden level and efficacy of PD-1/PD-L1 inhibitors in advanced non-small cell lung cancer: a systematic review and meta-analysis. *BMC cancer.* 2021. 21:1220
37.	Liu, Lihui, Bai, Hua, Seery, Samuel, Li, Sini, Wang, Chao, Xue, Pei, Zhao, Jie, Wang, Jie. Efficacy and safety of treatment modalities across *EGFR* selected/unselected populations with non-small cell lung cancer and brain metastases: A systematic review and Bayesian network meta-analysis. *Lung cancer (Amsterdam, Netherlands).* 2021. 158:74-84
38.	Wei, Y., Du, Q., Peng, X., Jin, J., Guo, H., Li, Y., Li, Q.. Effects of Clinicopathological Characteristics on the Survival of Patients Treated with PD-1/PD-L1 Inhibitor Monotherapy or Combination Therapy for Advanced Cancer: A Systemic Review and Meta-Analysis. Journal of Immunology Research. 2020. 2020:5269787
39.	Chen, J., Lu, W., Chen, M., Cai, Z., Zhan, P., Liu, X., Zhu, S., Ye, M., Lv, T., Lv, J., Song, Y., Wang, D.. Efficacy of immunotherapy in patients with oncogene-driven non-small-cell lung cancer: a systematic review and meta-analysis. Therapeutic Advances in Medical Oncology. 2024. 16
Ineligible comparator(s) (n = 8)	
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