CoLab Network

Health Technology Review

Overview of Systematic Reviews of Immune Checkpoint Inhibitors in Non–Small Cell Lung Cancer With *EGFR*, *ALK*, *ROS1*, and *RET* Actionable Driver Mutations

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Protocol

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Abbreviations

AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
ICI	immune checkpoint inhibitor
NMA	network meta-analysis
NSCLC	non–small cell lung cancer
PODET	Post-Market Drug Evaluation Team
RCT	randomized controlled trial
SR	systematic reviews

Introduction and Rationale

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) having been projected for 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 and accounts for more than 72% of newly diagnosed cases in Canada.[1,3] NSCLC is broadly categorized into 2 subtypes: squamous cell carcinoma and nonsquamous 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, nonsquamous 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 bones or the 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. More than 50% of NSCLC diagnoses in Canada are made at stage IV, with only about 23% 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 the *EGFR* gene, *ROS1* and *KRAS* mutations, *ALK* fusions, *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* 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]

Drugs targeting *EGFR*, *ROS1, NTRK, ALK,* and *RET* mutations in advanced or metastatic NSCLC have been recommended for reimbursement by CADTH and funded by the provinces; they are now available in the public health care systems in Canada. Conversely, drugs for *BRAF* V600, *KRAS* G12C, and *MET* exon 14 skipping mutations are available on the market in Canada but were not recommended for reimbursement or are not funded by the provinces. These latter drugs are only available to patients who are covered by private

insurance or who are willing to pay out of pocket. These drugs and their associated biomarkers are not a consideration for postmarket CADTH health technology reviews, such as the present report, which focus on policy-relevant health interventions.

Immune checkpoint inhibitor (ICI) drugs such as nivolumab, atezolizumab, and nivolumab are also available to treat NSCLC. They 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] The ICI drugs (such as nivolumab, pembrolizumab, and atezolizumab) were originally introduced into practice for patients with previously treated advanced or metastatic NSCLC; however, practice has evolved as the evidence base has developed. The immune checkpoint inhibitors pembrolizumab, nivolumab, atezolizumab, and cemiplimab are now more widely used as a first-line therapy in these patients.[18] Systemic pharmacotherapies such as ICIs can be given to patients who have either locally advanced disease that is confined to the chest area and nearby lymph nodes but is not amenable to surgery, or those who have metastatic disease that has spread to other organs. Systemic therapies can also be given in the adjuvant setting after surgery to reduce the risk of recurrence, and in the neoadjuvant setting before surgery to reduce tumour size.

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. Another key finding is that ICI drugs exhibit much smaller antitumour activity in cancers with these identified mutations than in their unmutated counterparts.[19-21] Consequently, Health Canada product monographs[22-24] and CADTH algorithms recommend the use of ICIs only after prior use of a targeted therapy and a course of platinum-based chemotherapy.[25-27] This has been translated into CADTH provisional funding algorithms for *ALK*, *EGFR*, and *RET* aberrations in NSCLC.[25-27] While clinical guidelines recommend using ICIs after targeted therapy and chemotherapy, uncertainties persist regarding their benefits in later lines of therapy and compared with alternative chemotherapy. In NSCLC, PD-L1 levels may predict response to ICI drugs but similar uncertainties persist.[28] Addressing this issue will involve assessing ICI effectiveness and safety in advanced NSCLC, considering specific driver mutations (i.e., *EGFR, ALK, RET,* and *ROS1*), and evaluating their place in the treatment sequence.

Project Scope and Protocol Development

The methodology will be an overview of systematic reviews (SRs) evaluating the efficacy and/or safety of ICI therapies in adults with advanced or metastatic NSCLC and actionable driver mutations.

Following the scoping and refinement process, CADTH and the Post-Market Drug Evaluation Team (PODET) at the University of Ottawa finalized the research and policy questions and selection criteria with content expert and jurisdictional input.

The protocol was developed by PODET in collaboration with CADTH and content experts. The protocol has been registered in PROSPERO (the International Prospective Register of Systematic Review). To inform

the final scope of this health technology assessment project, a draft protocol document was posted to the CADTH website for feedback, which will be considered when developing the final protocol.

Objectives

This review aims to provide a critical overview of the published SRs that compare the efficacy and safety of ICI monotherapies to other chemotherapeutic drugs in patients with advanced or metastatic NSCLC with specific mutations or chromosomal rearrangements (i.e., *EGFR*, *ALK*, *RET*, *ROS1*) who have experienced previous chemotherapy.

Deliverables

The following deliverables are planned:

- protocol
- scientific report
- summary and visual tool to aid knowledge dissemination.

Policy Questions

1. How should ICI monotherapies following chemotherapy be funded in patients with advanced or metastatic NSCLC that harbours actionable driver mutations (i.e., *ALK*, *EGFR*, *ROS1,* or *RET* genomic aberrations)?
2. Should all chemotherapy options be exhausted before fundingICI monotherapy?

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 *EGFR, ALK, RET,* and *ROS1* 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 *EGFR, ALK, RET,* and *ROS1* 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 the actionable driver mutations of interest?

Clinical Review Methods

The methodology will be an overview of SRs that evaluate the efficacy and/or safety of ICI therapies in adults with advanced or metastatic NSCLC and actionable driver mutations. The methodology employed for this review will follow the Cochrane Handbook guidance for conducting overviews of reviews.[29] This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols (PRISMA-P).[30]

Literature Search Methods

An experienced information specialist will develop and test the search strategies in an iterative fashion in consultation with the review team. Another senior information specialist will peer review the MEDLINE strategy before execution using the Peer Review of Electronic Search Strategies (PRESS) checklist.[31]

Using the multifile option and deduplication tool available on the Ovid platform, we will search Ovid MEDLINE ALL, Embase Classic and Embase, and the Cochrane Database of Systematic Reviews. We will use a combination of controlled vocabulary (e.g., *carcinoma*, *non–small cell lung*, *neoplasm metastasis*, *nivolumab*) and keywords (e.g., *NSCLC*, *metastatic*, *atezolizumab*). The vocabulary and syntax will be adjusted for each database as needed. We will apply an SR filter to the MEDLINE and Embase searches. Where possible, we will remove animal-only results, opinion pieces, conference abstracts, and another irrelevant publication types. No language limit will be applied but the results for all database searches will be limited to the publication years of 2013 to the present. We will download and deduplicate references in EndNote version 9.3.3 (Clarivate Analytics). After the searches are executed, the search will be updated monthly until the report has been reviewed by the relevant interested parties.

A search strategy is presented in Appendix 1.

Selection and Eligibility Criteria

Study Selection

Two reviewers will independently screen the titles and abstracts for all records for potentially relevant SRs (with or without meta-analysis) of randomized controlled trials (RCTs) or observational studies. The full text for any potentially relevant articles will be retrieved and independently assessed for possible inclusion based on the predetermined selection criteria (Table 1). Any disagreements will be discussed or adjudicated by a third reviewer. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. All records excluded at the full-text review stage will be documented in the final clinical report with reason for exclusion.

Selection Criteria

The selection criteria using a participant, intervention, comparator, outcome, and study design (PICOS) framework is defined in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Adults with advanced or metastatic NSCLC[a] with *RET* gene fusion, *ALK* gene rearrangement, *ROS1* mutation, or *EGFR* gene 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
Interventions	Atezolizumab, nivolumab, or pembrolizumab as monotherapy
Comparators	Docetaxel, gemcitabine, or pemetrexed as monotherapy or best supportive care[c]
Outcomes	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 type	Systematic reviews of RCTs[f]

NSCLC = non–small cell lung cancer.

[a]This refers to individuals with locally advanced NSCLC who are not candidates for surgical resection or definitive chemoradiation, or those 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 will expand consideration to patients who may have no current chemotherapy options remaining.

[d]This outcome focuses on change in total score. Additional subscale domains may be considered when total scores are not reported.

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

[f]Systematic reviews of, or including, nonrandomized studies were considered for populations or outcomes of interest only when no randomized controlled trial evidence was available.

To be included, eligible SRs must consider RCTs, 1 or more of the populations with a mutation of interest, and at least 1 intervention and comparator of interest. SRs with or without meta-analysis (or other quantitative synthesis approaches) are eligible.

Records reporting a protocol, conference abstracts, non-English records, non–systematic literature reviews, and eligible SRs not reporting any outcomes of interest will be excluded.

Data Extraction

A standardized data extraction form will be developed and reviewed by CADTH and a content expert. One reviewer will extract data and the extraction will be audited by a second reviewer. Pilot data extraction will be conducted on 2 of the included SRs and data extraction forms will be optimized before use.

From each SR, the following data will be 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 and any prognostic factors at baseline (e.g., treatment history, prior use of an 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 will be 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
- funding sources and author declarations.

Additional data to inform the SR quality assessment will also be extracted (e.g., reported methods, rationale for review inclusions, or limitations). Where other out-of-scope study data will be reported in a review, only data for our population, intervention, comparator, and outcomes of interest will be extracted. Efficacy and safety outcomes will be 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 will be provided in each SR.

Data from RCTs included by the SRs will be prioritized. Information will only be considered from nonrandomized studies when available and when a unique population or outcome not covered by the RCTs will be reported. Additionally, the overlap of the primary studies in the included SRs (i.e., multiple SRs of

the same primary studies) will be considered. Any important nuances and/or discrepancies in the reported outcomes or results will be descriptively summarized.

Quality Assessment

We will use AMSTAR (A MeaSurement Tool to Assess systematic Reviews) 2[32] to assess the methodological quality and risk of bias in the included SRs. AMSTAR 2 is intended to assess the following domains of SRs of both randomized and nonrandomized studies: description of the population, intervention, comparator, and outcome (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 review authors and funding sources.

The quality assessment will be completed by 1 reviewer and audited by a second reviewer. Any disagreements will be 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.[32] 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 1 weakness but no critical flaws; low indicates 1 critical flaw and possibly other identified weaknesses; and critical indicates the SR has more than 1 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 will be not having registered a protocol before the commencement of the review, inadequate literature search, lack of justification for excluded studies, and lack of risk of bias assessment for the studies included in the review. The strengths and limitations for each included review will be summarized alongside the overall ratings assessed.

For an SR involving a network meta-analysis (NMA), the confidence of the results will depend not only on the SR methods that can be assessed with the AMSTAR 2, but also on the analytic complexities in estimating specific pairwise effects in the NMA. The assumptions of goodness of fit of the model, homogeneity, and consistency will also be assessed.[33] No de novo risk of bias assessments will be conducted for the primary studies included in each review. We will summarize the author-assessed results for any reported risk of bias assessment of the eligible RCTs or nonrandomized studies included in each SR and summarize the reported strengths and limitations. We will additionally consider any discrepancies or deficiencies in the risk of bias assessments reported by the authors of the included SRs.

Data Analysis and Synthesis

A descriptive summary of the characteristics of the included reviews will be completed. For each population of interest (*RET* gene fusion, *ALK* gene rearrangement, *ROS1* mutation, or *EGFR* gene mutation), the results for each efficacy and safety outcome of interest will be summarized and synthesized narratively based on the author-reported findings across the SRs. The results will also be presented for any reported quantitative syntheses for all outcomes of interest, including all relative or absolute effects. For pairwise meta-analyses,

this will include the model (fixed effects or random-effects model), the meta-analytic estimates (such as the hazard ratio effect estimate and confidence interval), and measure of heterogeneity. For NMAs, this will include the probabilistic approach (Bayesian), the network meta-analytic estimates based on direct and indirect evidence (such as hazard ratio) and mean difference effect estimates and credible interval, and ranking methods such as the surface under the cumulative ranking curve for a treatment, which is a Bayesian summary of the ranking of multiple competing treatments and can be interpreted as the estimated proportion of treatments worse than the treatment of interest. No new quantitative syntheses will be planned (e.g., meta-analysis of individual or aggregate study results). Data for each actionable driver mutation will be considered separately when summarizing the quantitative results extracted from the included SRs.

Opportunities for Feedback

Interested parties will be given the opportunity to provide feedback on the draft report. Data identified as part of the feedback process may only be included if the source of the data is in the public domain and the data are within scope.

Areas for Potential Amendments

All protocol amendments will be documented and reported in the final report.

References

1. Canadian cancer statistics. Toronto (ON): Canadian Cancer Cancer Advisory Committee; 2021: https://cdn.cancer.ca/-/media/files/research/cancer-statistics/2021-statistics/2021-pdf-en-final.pdf. Accessed 2022 Jan 5.
2. Cancer.Net American Society of Clinical Oncology (ASCO). Lung cancer - non-small cell: statistics. 2021; https://www.cancer.net/cancer-types/lung-cancer-non-small-cell/statistics. Accessed 2022 Jan 12.
3. National Cancer Institute. Non-small cell lung cancer treatment (PDQ®) – health professional version. 2021; https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq. Accessed 2021 Dec 4.
4. Yakut T, Schulten H-J, Demir A, et al. Assessment of molecular events in squamous and non-squamous cell lung carcinoma. *Lung Cancer.* 2006;54(3):293-301. PubMed
5. Socinski MA, Obasaju C, Gandara D, et al. Clinicopathologic features of advanced squamous NSCLC. *J Thorac Oncol.* 2016;11(9):1411-1422. PubMed
6. Bansal P, Osman D, Gan GN, Simon GR, Boumber Y. Recent advances in targetable therapeutics in metastatic non-squamous NSCLC. *Front Oncol.* 2016;6:195170. PubMed
7. Lung Cancer Canada. Lung cancer staging in Canada. 2020; https://www.lungcancercanada.ca/Lung-Cancer/Staging.aspx. Accessed 2021 Dec 4.
8. Iyer S, Roughley A, Rider A, Taylor-Stokes G. The symptom burden of non-small cell lung cancer in the USA: a real-world cross-sectional study. *Support Care Cancer.* 2014;22(1):181-187. PubMed
9. National Comprehensive Cancer Network (NCCN). Non-small cell lung cancer. NCCN Clinical Practice Guidelines in Oncology. 2021; https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1450. Accessed 2021 Dec 4.
10. Planchard D, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Lugano (CH): European Society for Medical Oncology; 2020: https://www.esmo.org/content/download/347819/6934778/1/ESMO-CPG-mNSCLC-15SEPT2020.pdf. Accessed 2021 Dec 4.
11. Ellis PM, Vella ET, Ung YC. Systemic treatment for patients with advanced non-small cell lung cancer. *(Guideline 7-10, version 3)*. Toronto (ON): Cancer Care Ontario; 2016: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31811. Accessed 2021 Dec 4.
12. Cascetta P, Sforza V, Manzo A, et al. RET inhibitors in non-small-cell lung cancer. *Cancers (Basel).* 2021;13(17):01.
13. Davies KD, Le AT, Theodoro MF, et al. Identifying and targeting ROS1 gene fusions in non-small cell lung cancer. *Clin Cancer Res.* 2012;18(17):4570–4579. PubMed
14. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA.* 2014;311(19):1998-2006. PubMed
15. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* 2010;363(18):1693-1703. PubMed
16. Shaw AT, Solomon BJ, Besse B, et al. ALK Resistance Mutations and Efficacy of Lorlatinib in Advanced Anaplastic Lymphoma Kinase-Positive Non–Small-Cell Lung Cancer. *J Clin Oncol.* 2019;37(16):1370-1379. PubMed
17. Dempke WCM, Fenchel K, Uciechowski P, Dale SP. Second-and third-generation drugs for immuno-oncology treatment—the more the better? *Eur J Cancer.* 2017;74:55-72. PubMed
18. Jaiyesimi IA, Leighl NB, Ismaila N, et al. Therapy for Stage IV Non–Small Cell Lung Cancer Without Driver Alterations: ASCO Living Guideline, Version 2023.3. *J Clin Oncol.* 2024.
19. Dantoing E, Piton N, Salaün M, Thiberville L, Guisier F. Anti-PD1/PD-L1 Immunotherapy for Non-Small Cell Lung Cancer with Actionable Oncogenic Driver Mutations. *Int J Mol Sci.* 2021;22(12):6288. PubMed
20. Mazieres J, Drilon A, Lusque A, et al. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol.* 2019;30(8):1321–1328. PubMed

21. Luciani A, Ghidini A, Borgonovo K, Parati MC, Petrelli F. Outcome of non-small-cell lung cancer with driven mutations treated with anti-PD-(L)1 agents: A systematic review. *Tumori.* 2022;3008916221122601. PubMed

22. Keytruda (pembrolizumab): solution for infusion 100 mg/4 mL vial [product monograph]. Kirkland (QC): Merck Canada Inc.; 2024 Aug 7: https://pdf.hres.ca/dpd_pm/00071768.PDF. Accessed 2024 Jan 9.

23. Opdivo (nivolumab): Intravenous Infusion, 10 mg nivolumab /mL 40 mg and 100 mg single-use vials [product monograph]. Saint-Laurent (QC): Bristol-Myers Squibb Canada; 2024 Jun 28: https://pdf.hres.ca/dpd_pm/00070041.PDF. Accessed 2024 Jan 9.

24. Tecentriq (atezolizumab): concentrate for solution for infusion, 60 mg/mL 1200 mg/20 mL and 840 mg/14 mL single use vials for intravenous infusion [product monograph]. . Mississauga (ON): Hoffmann-La Roche Ltd.; 2024 Mar 13: https://pdf.hres.ca/dpd_pm/00071423.PDF. Accessed 2024 Jan 9.

25. Provisional Funding Algorithm. Indication: Anaplastic Lymphoma Kinase–Positive Non–Small Cell Lung Cancer. *(CADTH Reimbursement Review)*. Ottawa (ON): CADTH; 2022: https://www.cadth.ca/sites/default/files/pdf/PH0009-ALK%2BNSCLC-Algorithm.pdf. Accessed 2023 Aug 16.

26. Provisional Funding Algorithm. Indication: Advanced or Metastatic Non–Small Cell Lung Cancer with activating epidermal growth factor receptor mutations. *(CADTH Reimbursement Review)*. Ottawa (ON): CADTH; 2023: https://www.cadth.ca/sites/default/files/DRR/2023/PH0028-NSCLC-EGFR.pdf. Accessed 2023 Aug 16.

27. Provisional Funding Algorithm. Indication: RET fusion-positive Non–Small Cell Lung Cancer. *(CADTH Reimbursement Review)*. Ottawa (ON): CADTH; 2023: https://www.cadth.ca/sites/default/files/DRR/2023/PH0026-Implementation-Advice-Report-Algorithm-RET-Positive-NSCLC.pdf. Accessed 2023 Aug 16.

28. Passiglia F, Bronte G, Bazan V, et al. PD-L1 expression as predictive biomarker in patients with NSCLC: a pooled analysis. *Oncotarget.* 2016;7(15):19738. PubMed

29. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019;10(10):ED000142. PubMed

30. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 2015;4(1):1. PubMed

31. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *J Clin Epidemiol*. 2016;75:40-46. PubMed

32. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ*. 2017;358:j4008. PubMed

33. Donegan S, Williamson P, D'Alessandro U, Tudur Smith C. Assessing key assumptions of network meta-analysis: a review of methods. *Res Synth Methods*. 2013;4(4):291-323. PubMed

Appendix 1: Literature Search Strategy

Note this appendix has not been copy-edited.

[20 Dec 2023]

MEDLINE

Database: Ovid MEDLINE(R) ALL < 1946 to December 19, 2023 >

Search Strategy

1. Carcinoma, Non-Small-Cell Lung/ (72661)
2. (Squamous Cell Carcinoma/ or Adenocarcinoma/ or Large Cell Carcinoma/) and exp Lung Neoplasms/ (41206)
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. (96791)
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. (35413)
5. (NSCLC or NSCLCs).tw,kw,kf. (63198)
6. or/1-5 [**NSCLC**] (157856)
7. exp Neoplasm Metastasis/ (222706)
8. Neoplasm Recurrence, Local/ (146769)
9. (meta adj sta*).tw,kw,kf. (689)
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. (5058314)
11. (late? adj2 stage?).tw,kw,kf. (78429)
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. (203849)
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. (501897)
14. or/7-13 [**ADVANCED/METASTATIC CANCER**] (5676952)
15. 6 and 14 [**NSCLC - ADVANCED/METASTATIC**] (90549)

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. (6373)
17. Nivolumab/ (5436)
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. (10193)
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. (8856)
20. Immune Checkpoint Inhibitors/ (9557)
21. ((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. (41389)
22. ((ICI or ICIs) adj5 immun*).tw,kw,kf. (10262)
23. or/16-22 [**DRUGS OF INTEREST, DRUG CLASS**] (53294)
24. 15 and 23 [**ADVANCED/METASTATIC NSCLC - DRUGS/DRUG CLASS OF INTEREST**] (6617)
25. exp Animals/ not Humans/ (5180113)
26. 24 not 25 [**ANIMAL-ONLY REMOVED**] (6579)
27. (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. (2593796)
28. 26 not 27 [**OPINION PIECES, PUBLICATION TYPES NOT OF INTEREST REMOVED**] (6419)
29. Systematic Review.pt. (247886)
30. exp Systematic Reviews as Topic/ (12298)
31. Meta Analysis.pt. (191988)
32. exp Meta-Analysis as Topic/ (28811)
33. (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. (298702)

34. (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. (398916)
35. exp Technology Assessment, Biomedical/ (12244)
36. (cochrane or health technology assessment or evidence report or systematic reviews).jw. (23079)
37. Network Meta-Analysis/ (5574)
38. (network adj (MA or MAs)).tw,kw,kf. (20)
39. (NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw,kf. (9943)
40. indirect* compar*.tw,kw,kf. (2947)
41. (indirect treatment* adj1 compar*).tw,kw,kf. (508)
42. (mixed treatment* adj1 compar*).tw,kw,kf. (526)
43. (multiple treatment* adj1 compar*).tw,kw,kf. (234)
44. (multi-treatment* adj1 compar*).tw,kw,kf. (4)
45. simultaneous* compar*.tw,kw,kf. (1340)
46. mixed comparison?.tw,kw,kf. (46)
47. or/29-46 [**SR FILTER**] (595580)
48. 28 and 47 [**ADVANCED/METASTATIC NSCLC - DRUGS/DRUG CLASS OF INTEREST - SRs**] (513)
49. limit 48 to yr=”2013-current” (**513**).

Appendix 2: Version and Revision History

Note this appendix has not been copy-edited.

Periodically, this document will be revised as part of ongoing process improvement activities and methods updates. The following version control table, as well as the version number and date on the cover page, is to be updated when any changes are made.

Table 2: Version and Revision History

Version	Description of Changes	Prepared By	Date
Draft	Draft protocol and MEDLINE search strategy (still requires PRESS and multidatabase strategy)	PODET	December 21, 2023
Revised draft	Draft reflecting changes based on feedback and comments from CADTH	PODET	January 9, 2024
Revised draft	Draft reflecting changes based on external feedback.	PODET	February 28, 2024, with further refinement March 6, 2024
Final	Protocol updated to align content with associated final report, PROSPERO number inserted.	PODET	August 27, 2024

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