CoLab Network

Health Technology Review

Overview of Systematic Reviews of Immunotherapy in Non–Small-Cell Lung Cancer With Actionable Driver Mutations

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This health technology review is being conducted by the Post-market Drug Evaluation Team (PODET) through the Post Market Drug Evaluation CoLab Network.

PROSPERO Registration Number: Pending Submission

Draft Protocol

Table of Contents

Abbreviations 4

Introduction and Rationale 5

Project Scope and Protocol Development 6

Objectives 6

Deliverables 6

Policy Questions 7

Research Questions 7

Clinical Review Methods 7

Literature Search Methods 7

Selection and Eligibility Criteria 8

Data Extraction 9

Quality Assessment 10

Data Analysis and Synthesis 10

Opportunities for Stakeholder Feedback 10

Areas for Potential Amendments 10

References 11

Appendix 1: Literature Search Strategy 13

Appendix 2: Version and Revision History 16

List of Tables

Table 1: Selection Criteria 8
Table 2: Version and Revision History 16

Abbreviations

AMSTAR 2	A MeaSurement Tool to Assess systematic Reviews 2
IO	immuno-oncology
NSCLC	non–small-cell lung cancer
PODET	Post-Market Drug Evaluation Team

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) 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]

Early diagnosis improves prognosis and patient responsiveness to therapy. Diagnosis is based on histology and symptom presentation.[3,4] 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 burden 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.[5,6] Staging at diagnosis is key in determining disease prognosis and facilitates treatment selection.[3,6] 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 5-year survival of NSCLC varies depending on the stage but on average, the estimated 5-year survival for NSCLC is 25%.[7]

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 *EGFR* gene, *ROS1*, *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.[6,8,9] Prevalence estimates from studies show that about 1% to 2% of NSCLC cases are *RET* fusion positive,[10] 1% are *ROS1* fusion positive,[11] 17% have activating mutations in the *EGFR* gene,[12] and 5% have an *ALK* rearrangement.[13,14]

Evidence has shown that tumours bearing specific mutations and treated with targeted therapies will respond well to treatment. As such, it is widely recommended to first treat tumours bearing actionable mutations with targeted therapies. This has been translated into CADTH provisional funding algorithms for *ALK*, *EGFR,* and *RET* aberrations in NSCLC.[15-17] Another key finding is that immuno-oncology (IO) drugs such as programmed cell death 1 (PD-1) or programmed cell death 1 ligand 1 (PD-L1) blockers exhibit much smaller antitumour activity in cancers with these identified mutations than in their unmutated counterparts.[18-20] Consequently, Health Canada product monographs[21-23] and CADTH algorithms recommend use of IOs only after prior use of a targeted therapy and a course of platinum-based chemotherapy.[15-17]

Currently, IO monotherapy with atezolizumab, nivolumab, or pembrolizumab is indicated for advanced or metastatic NSCLC regardless of mutational status, following prior chemotherapy. Given the growth of

publications (including systematic reviews[24]) on this topic, there is no overall consensus on the use of IOs in the third-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, the aim of this review is to provide a critical overview of the published systematic reviews that compare the efficacy and safety of IOs to other chemotherapeutic drugs in patients with advanced or metastatic NSCLC with specific mutations or chromosomal rearrangements.

Project Scope and Protocol Development

The methodology employed for this review follows the guidelines outlined in the Cochrane Handbook.[25] Reporting of the protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols (PRISMA-P).[26]

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 will be submitted for registration in PROSPERO (the International Prospective Register of Systematic Review). To inform the final scope of this health technology assessment project, a draft protocol document will be posted to the CADTH website for stakeholder feedback, which will be considered when developing the final protocol.

Objectives

The main objective of this review is to summarize the current evidence reported in systematic reviews regarding the efficacy and safety of IO therapies for adults with advanced or metastatic NSCLC previously treated with a platinum-based chemotherapy who have actionable driver mutations.

Deliverables

The following deliverables are planned:

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

Policy Questions

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

Research Questions

1. What is the evidence for the clinical efficacy and effectiveness of atezolizumab, nivolumab, and pembrolizumab monotherapy in patients with advanced or metastatic NSCLC with actionable driver mutations that has failed with 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 has failed with 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?

Clinical Review Methods

The methodology will be an overview of systematic reviews evaluating the efficacy and/or safety of IO 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.[25] This protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Protocols (PRISMA-P).[27]

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.[28]

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 utilize 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 a systematic review 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 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).

Selection and Eligibility Criteria

Study Selection

Two reviewers will independently screen the titles and abstracts for all records for potentially relevant systematic reviews (with or without meta-analysis) of randomized controlled trials 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.

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. Subgroups Mutation: • *ALK* • *EGFR* • *ROS1* • *RET* 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
Outcomes	Efficacy outcomes: • Overall survival • Progression-free survival • Objective response rate • Quality of life or health-related quality of life[b] Safety outcomes: • Total number of adverse events

Criteria	Description
	• 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 • Withdrawals due to adverse events • Mortality
Study type	Systematic reviews

NSCLC = non–small-cell lung cancer; PD-L1 = programmed death cell 1 ligand 1.

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

To be included, eligible systematic reviews must consider 1 or more of the populations with a mutation of interest and at least 1 intervention and comparator of interest. Systematic reviews 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 systematic reviews not reporting any outcomes of interest will be excluded.

Data Extraction

One reviewer will extract data and a second independent reviewer will assess all extracted datasets for completeness and accuracy. Pilot data extraction will be conducted on 2 included systematic reviews and standardized extraction forms will be created and used (DistillerSR, Evidence Partners).

The following data will be extracted from each eligible systematic review: basic characteristics, including eligibility criteria, search details and/or limits, designs of included studies, number of included studies, total number of patients and bibliographic information; details on patients, interventions, controls, and outcomes (including any definitions applied, treatment history, number of previous therapies, stage at diagnosis, smoking status at diagnosis); synthesized results, including the descriptive or pooled summary effects of each comparison for each outcome if meta-analysis were conducted (including associated measures of variation or precision if applicable); results from the risk of bias assessments completed for primary studies; authors' conclusions; and funding sources and author declarations. Data for populations or outcomes from the included systematic reviews that is considered out of scope will not be extracted. Additional data that may inform the quality assessment may also be extracted.

We will additionally consider the overlap of the primary studies in the included systematic reviews (i.e., multiple systematic reviews of the same primary randomized controlled trials) using the amount of overlap (%), our assessed quality of the systematic review, and the recency of the review or evidence contained. We will descriptively summarize any important nuances and/or discrepancies in the outcomes or results reported.

Quality Assessment

We will use AMSTAR (A MeaSurement Tool to Assess systematic Reviews) 2[29] to assess the methodological quality and risk of bias in the included systematic reviews. AMSTAR 2 is intended to assess the following domains of systematic reviews of both randomized and nonrandomized studies: 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. The quality assessment will be completed by 1 reviewer and validated by a second reviewer. Any disagreements will be resolved by discussion. An overall rating will be considered following the related AMSTAR 2 guidance and the strengths and/or weaknesses for each included review will be summarized.

Data Analysis and Synthesis

A descriptive summary of the main characteristics of the included reviews will be completed. For each efficacy and safety outcome of interest, the clinical evidence will be summarized and synthesized narratively based on the findings of the systematic review and presented alongside any relevant quantitative evidence or effects reported.

Results will be summarized at the aggregate level by the whole population of interest (*RET* gene fusion, *ALK* gene rearrangement, *ROS1* mutation, or *EGFR* gene mutation) and for subgroups by mutation and programmed cell death 1 ligand 1 (PD-L1) expression (i.e., less than 1%; 1% and higher; 50% and higher).

Opportunities for Stakeholder Feedback

Stakeholders 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 are in the public domain and is within scope.

Areas for Potential Amendments

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

References

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22. [Internet]. Ottawa (ON): Merck Canada Inc.; 2023 [updated 2023 DEC 29; cited 2024 JAN 09]. OPDIVO (nivolumab) [product monograph]. Available from: https://health-products.canada.ca/. Also available in paper copy from the publisher.

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Appendix 1: Literature Search Strategy

[20 Dec 2023]

MEDLINE Draft

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

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

PODET = Post-Market Drug Evaluation Team.

This health technology review is being conducted by the Post-market Drug Evaluation Team (PODET) through the Post Market Drug Evaluation CoLab Network. This work was supported by CADTH and its Post-Market Drug Evaluation Program, through funding provided by Health Canada.