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CoLab Network

Summary Report

Immune Checkpoint Inhibitors for Non–Small Cell Lung Cancer With Actionable Driver Mutations

Drug Utilization Report Authors

Qi Guan, Suriya J Aktar, Reka E Pataky, Mariet Mathew Stephen, Maud Marques, Karen Gambaro, Kahina Rachedi, Katharina Forster, Samara Strub, Nicola Bai, Tamer Jareda, Christie Farrer, Scott Gavura, Winson Y Cheung, Stuart Peacock, Mina Tadrous, Cheryl Ho, Vishal Navani, Kelvin KW Chan

Systematic Review Report Authors

Shariq Najeeb, Said Yousef Abdelrazeq, Shannon E. Kelly, Xiaoqin Wang, Becky Skidmore, Nazmun Nahar, Melissa Brouwers, George A. Wells

The Drug Utilization Study was conducted by the Canadian Cancer Real-world Evaluation (CCRE) team in partnership with Exactis Innovation, and the Review of Systematic Reviews was conducted by the POst-Market Drug Evaluation Team (PODET), both through the Post-Market Drug Evaluation (PMDE) CoLab Network.

Executive Summary

Lung cancer is the most frequently diagnosed cancer in Canada and the primary cause of cancer-related deaths. Treatments for advanced non-small cell lung cancer (NSCLC) now include targeted therapies and immunotherapy. However, it's still uncertain how effective immune checkpoint inhibitor (ICI) monotherapy is when given as monotherapy after use of targeted therapy and chemotherapy.

A drug utilization study and a review of systematic studies aimed at understanding real-world treatment patterns and the efficacy and safety of ICIs in patients with advanced NSCLC with actionable driver mutations were conducted.

Researchers found that targeted therapy was the most frequently used treatment in the first to third exposures for all included provinces, and that ICIs were not frequently used early on but increased in third and fourth exposures. The research also revealed that ICIs alone as second-line therapy did not significantly benefit patients with NSCLC with *EGFR* gene mutation when compared to chemotherapy. There is a lack of evidence on the efficacy of second-line (or beyond) ICIs in patients with NSCLC with other gene mutations. However, the studies had some limitations, and the findings should be interpreted with caution.

Background

Lung cancer is the most frequently diagnosed cancer in Canada and the leading cause of cancer-related deaths. The overall 5-year survival rate for patients with NSCLC is approximately 25%, with survival decreasing to 9% for patients with advanced stage disease.

Treatments for advanced NSCLC have expanded in recent years to include targeted therapies and immunotherapy, in addition to standard chemotherapy. Specific driver mutations in oncogenes (such as *EGFR*, *ROS1*, *RET*, *ALK*, and *KRAS*) play a big role in tumour growth, and treatments have been developed to target the products of these mutations, known as targeted therapies. Immunotherapy with ICIs has shown effectiveness in treating advanced NSCLC by increasing patients' immune defences against tumours, but may be less effective for tumours with certain mutations.

Policy Issue

ICI treatment alone (monotherapy) is currently approved and funded for the treatment of advanced NSCLC with actionable driver mutations after patients have received targeted therapies as well as chemotherapy. However, it remains unclear if ICI monotherapy is beneficial in this setting.

Policy Questions

1. How should ICI monotherapies following chemotherapy be funded in patients with advanced or metastatic NSCLC harbouring actionable driver mutations, specifically *ALK*, *EGFR*, *ROS1*, or *RET* genomic aberrations?
2. Should all chemotherapy options be exhausted before funding ICI monotherapy?

Objectives

The objective of the drug utilization study was to determine real-world treatment patterns in patients with advanced NSCLC with *ALK*, *EGFR*, *ROS1*, or *RET* genomic aberrations. A secondary objective of the drug utilization study was to determine the feasibility of conducting an observational study to compare the effectiveness of subsequent ICI and subsequent single-drug chemotherapy in this population.

The objective of the Review of Systematic Reviews was to determine the efficacy and safety of ICIs (atezolizumab, pembrolizumab, nivolumab) in these patients who did not respond well to previous chemotherapy.

Findings

Drug Utilization

Researchers identified 4,222 patients who received publicly funded targeted therapy as first-line treatment for NSCLC. The data were gathered from the Canadian Cancer Real-world Evaluation Platform for Ontario, British Columbia, and Alberta, and from patients captured in the Personalize My Treatment Registry who were treated in Quebec, New Brunswick, and Nova Scotia. On average, patients were in their mid-60s when starting targeted therapy and the majority were female.

The researchers tracked up to 4 treatment exposures to determine the typical treatment sequence. They found that:

- Targeted therapy was the most frequently used treatment in the first to third exposures in all included provinces.
- In the majority of second exposure targeted therapy cases, patients switched from a non-osimertinib targeted therapy to osimertinib.
- A small number of patients in each province received ICI second-line after first-line targeted therapy.
- Targeted therapy decreased in the fourth exposure, with single-drug chemotherapy and ICIs increasing.

The number of patients who received ICIs in the third exposure is too small to support a comparative study examining their effectiveness against other treatment options.

Efficacy and Safety

Researchers identified 13 systematic reviews of randomized controlled trials examining the efficacy and safety of ICIs in patients with advanced NSCLC with actionable driver mutations who did not respond well to previous chemotherapy and were treated with ICIs.

All 13 systematic reviews reported on overall survival (time from treatment to death from any cause) and progression-free survival (time from treatment to disease progression or death) for patients with NSCLC who were positive for an *EGFR* gene mutation. No other efficacy or safety outcomes or populations were reported, except for one systematic review that looked at *EGFR* positive patients with different levels of PD-L1 expression.

The findings from the 13 systematic reviews suggest that:

- ICIs alone as second-line therapy or beyond do not significantly benefit patients with NSCLC with *EGFR* gene mutation when compared to chemotherapy.
- ICIs may be more beneficial in patients with *EGFR* mutations with high PD-L1 expression levels (PD-L1 of 5% or more rather than less than 5%).

None of the included systematic reviews specifically examined the relative harms and safety profile of ICI monotherapies in patients with *EGFR*-mutated NSCLC previously exposed to chemotherapy. However, safety in this patient population is not expected to differ significantly from patients with unmutated NSCLC. There was no evidence on other mutations of interest.

The results from these 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.

Limitations

There were a few key limitations to both the drug utilization study and the review of systematic reports.

The data in the drug utilization study only captures publicly funded NSCLC treatments in certain provinces, which may not be representative of the entire population. Additionally, patient biomarker status could not be identified in Ontario, Alberta, or British Columbia. Researchers used exposure to targeted therapy as a proxy for mutation status.

The main limitations of the review was the lack of clinical evidence for any *ALK*-, *RET*-, or *ROS1*-positive patients, the methodological quality of the included systematic reviews, and the lack of clinical evidence to draw conclusions about the safety of the interventions in any population of interest. Readers should use caution when reviewing and interpreting these results.

Implications for Policy-Making

The drug utilization study found that only a small proportion of patients with NSCLC receive ICI treatment after their first-line targeted therapy. While this is a small portion of the population, it may be valuable to assess the effectiveness of this treatment sequence. However, conducting a comparative analysis on the safety and effectiveness of using ICI in this context is not currently feasible due to the small proportion of patients. For patients who receive further treatments after first-line targeted therapy, the most common options for subsequent treatments are different targeted therapies and platinum doublet chemotherapy.

Based on the systematic reviews included in the review, ICI monotherapy is unlikely to significantly improve overall survival and progression-free survival compared to chemotherapy in patients with *EGFR*-mutated NSCLC who have received prior therapy. Based on the lack of evidence, the efficacy of these drugs in patients with NSCLC who have received previous therapy and are positive for *ROS1*, *RET*, and *ALK* remains uncertain. It is challenging to determine the safety of ICIs in patients with actionable mutations, as the safety profile was not examined for these patients in the studies considered. Despite this uncertainty, there is no reason to believe the safety profile would be any different in this subpopulation of patients.

The studies included in the systematic reviews did not include patients previously treated with targeted therapy, unlike the population reported in the drug utilization study. It is unclear how the clinical evidence can be generalizable to the population of interest identified in the administrative data across Canada and relevant to policy-makers.

Taken together, these studies suggest that the scarce utilization of ICIs in *EGFR*-mutated NSCLC as seen in the population in Canada is consistent with the expectation of a limited clinical benefit as reported in the scientific literature.

Considerations

Post-Market Drug Evaluation (PMDE) projects aim to produce health policy issue evidence and are not linked to a recommendation.

This work was intended to inform health policy. Clinical questions regarding NSCLC treatment should be directed to a health care professional.

For more information on CoLab and its work visit colab.cda-amc.ca

Full scientific reports:

Utilization of Cancer Therapies for Advanced Non-Small-Cell Lung Cancer With an Oncogenic Driver Mutation

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

This work was conducted by the Canadian Cancer Real-world Evaluation (CCRE) team, Exactis Innovation, and the POst-Market Drug Evaluation Team (PODET) through the Post-Market Drug Evaluation CoLab Network. It was supported by Canada's Drug Agency (CDA-AMC) and its Post-Market Drug Evaluation Program through funding provided by Health Canada.

CDA-AMC is a pan-Canadian health organization. Created and funded by Canada's federal, provincial, and territorial governments, we're responsible for driving better coordination, alignment, and public value within Canada's drug and health technology landscape. We provide Canada's health system leaders with independent evidence and advice so they can make informed drug, health technology, and health system decisions, and we collaborate with national and international partners to enhance our collective impact.

CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with the Post-Market Drug Evaluation Program to produce credible and timely evidence on postmarket drug safety and effectiveness.

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