CoLab Network

Observational Study

# Utilization of Immunotherapy After Targeted Therapies for Non–Small Cell Lung Cancer

Final Project Protocol (April 4, 2024)

September 2024

## Abstract

Lung cancer is among the most frequently diagnosed cancers in Canada and is a leading cause of cancer-related deaths. For patients with non–small cell lung cancer (NSCLC) whose tumours bear actionable driver mutations (*ALK*, *EGFR*, *RET*, *ROS1* positive mutations), targeted therapies are an effective first-line treatment. Health Canada has recommended the use of immunotherapies after treatment with targeted therapies followed by platinum-based chemotherapy among patients with actionable driver mutations. However, the real-world sequence of treatments following targeted therapy is unclear, and there remains uncertainty as to whether there are any substantial benefits to using subsequent immunotherapy treatments in this patient population. Therefore, the Canadian Cancer Real-world Evaluation Platform, in collaboration with Exactis Innovation, will conduct a utilization study on patients with advanced NSCLC who receive first-line targeted therapy to determine the sequence of treatments for this patient population in the real world. The results of this study will be used to determine the feasibility of an observational study examining the effectiveness of subsequent immunotherapy versus single-agent chemotherapy.

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# Abbreviations

| | |
|---|---|
| **ICI** | immune checkpoint inhibitor |
| **NSCLC** | non–small cell lung cancer |

# Project Team

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# Amendments and Updates

## Table 1: Version History

| Version | Version date | Location (e.g., heading or page) | Amendment description and rationale |
|---|---|---|---|
| 1 | January 12, 2024 | NA – first draft | NA – first draft |
| 2 | February 22, 2024 | Throughout document | Incorporating feedback from PMDE clinical experts |
| 3 | March 14, 2024 | Research methods | Altered cohort exclusion criteria, removed erlotinib from list of targeted therapies, confirmed surgical and histology codes |
| 4 | April 4, 2024 | Throughout document | Updated variable definitions; added new team member |

NA = not applicable; PMDE = Post-Market Drug Evaluation.

# Background and Rationale

## Condition

Lung cancer is the most frequently diagnosed cancer in Canada and the leading cause of cancer-related deaths.[1] There were 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 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, or hoarseness at clinical presentation.[1,3] In advanced or metastatic disease, patients experience additional symptom burden, such as trouble 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 also challenging for disease management in real-world practice. Unfortunately, almost 50% of NSCLC diagnoses in Canada are made at stage IV, with only approximately 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]

### Treatments

The expression of genome 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* (epidermal growth factor receptor) gene mutations, *ROS1* (C-ROS oncogene 1) and *RET* fusions, *KRAS* (Kristen rat sarcoma viral oncogene homologue) G12C mutation, *ALK* (anaplastic lymphoma kinase) fusions, *BRAF* V600E mutation, and others. These discoveries greatly influenced treatment strategies in practice, improved patient quality of life, and increased overall survival for patients.[6,8,9] Prevalence estimates from studies show that approximately 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]

Tumours bearing specific mutations respond well to treatment using targeted therapies; therefore, such treatments are widely recommended in the first-line setting for patients who have tumours bearing actionable driver mutations. Although immune checkpoint inhibitors (ICIs) such as PD-1 or PD-L1 blockers have exhibited substantial benefit for the treatment of some cancers, evidence has shown that they may be less effective for tumours bearing specific mutations.[15-17] Consequently, Health Canada and CADTH have recommended the use of ICIs only after prior use of targeted therapy and a course of chemotherapy.[18-20]

### Gaps in Knowledge

It is unclear whether there are any substantial benefits to using ICIs in the third-line setting or beyond for such patients (i.e., after targeted therapy and chemotherapy) or beyond for patients with NSCLC bearing oncogenic driver mutations, and how this treatment may compare with other third-line (or beyond) treatment options such as pemetrexed. The purpose of study is to describe the real-world utilization and sequencing of treatment regimens for patients who received first-line driver mutation–targeted therapies and determine the number of patients with advanced NSCLC bearing actionable driver mutations who receive ICI or single-agent chemotherapy in subsequent lines of therapy.

### Expected Contribution of This Study

The results of this study will describe current treatment patterns for patients who received first-line targeted therapies to treat NSCLC with actionable oncogenic driver mutations and inform the feasibility of a study comparing the effectiveness between 2 exposure groups — subsequent ICI versus single-agent chemotherapy — in an observational study using health administrative data.

## Policy Questions

1. How should ICI monotherapies post chemotherapy be funded in patients with advanced or metastatic NSCLC harbouring actionable driver mutations?
2. Should all chemotherapy options be exhausted before funding ICI monotherapy?

# Policy Impact

The findings of this study will be used to determine the current utilization and treatment patterns and inform the feasibility of a future observational study comparing effectiveness of ICI versus single-agent chemotherapy subsequent to first-line targeted therapy.

# Research Question

1. What is the utilization of first-line targeted therapy and subsequent lines of therapy for the treatment of advanced NSCLC among patients with actionable driver mutations?

# Research Question 1

## Table 2: Study Objective

| Study component | Description |
|---|---|
| Objective | To describe real-world utilization of driver mutation–targeted first-line therapies for NSCLC and post–first-line treatments for patients with advanced NSCLC who received first-line targeted therapy. |
| Population | Individuals 18 years and older who start first-line targeted therapy for the treatment of advanced NSCLC. |
| Drug utilization measures | Rates and proportions of driver mutation–specific first-line targeted therapies; rates and proportions of identified subsequent (to identified first-line targeted therapies) therapies |
| Patient characteristics and subgroups | **Descriptive**: Clinical and demographic characteristics |
| Time | **Accrual period:**<br>• January 1, 2014, to October 31, 2022 (Ontario)<br>• January 1, 2014, to September 30, 2022 (Alberta)<br>• October 1, 2010, to December 31, 2021 (British Columbia)<br>• April 1, 2011, to December 31, 2022 (Exactis cohort: Quebec, New Brunswick, Nova Scotia)<br>**Observation period:**<br>• Between date of first-line targeted therapy start (index date) and October 31, 2023 (Ontario)<br>• Between date of first-line targeted therapy start (index date) and December 31, 2022 (Alberta)<br>• Between date of first-line targeted therapy start (index date) and December 31, 2022 (British Columbia)<br>• Between date of first-line targeted therapy start (index date) and December 31, 2023 (Exactis cohort: Quebec, New Brunswick, Nova Scotia)<br>• Patients are followed until death or end of study period (date differs between provinces) |
| Setting | This study will examine patients in the outpatient setting in Ontario, Alberta, British Columbia, Quebec, New Brunswick, and Nova Scotia. |
| Main measure of effect | The numbers and proportions of patients with advanced NSCLC receiving specified first-line and post–first-line anticancer therapies (especially immunotherapy) |

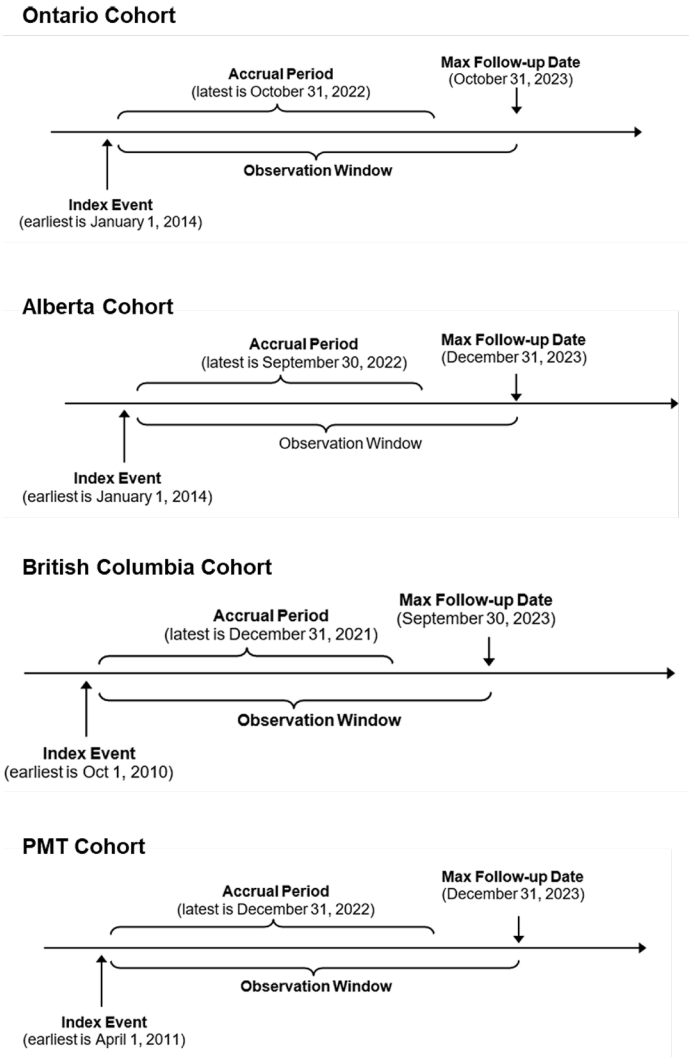
NSCLC = non–small-cell lung cancer.

# Research Methods

## Study Design

Retrospective drug utilization study.

## Figure 1: Study Design Diagrams for Each Study Site




PMT = Personalize My Treatment.

## Table 3: Key Dates for Study Design by Province

| Study design details | Key dates | | | |
|---|---|---|---|---|
| | Ontario | Alberta | British Columbia | Exactis cohort (Quebec, New Brunswick, Nova Scotia) |
| Accrual window for patients on first-line targeted therapy | January 1, 2014, to October 31, 2022 | January 1, 2014, to September 30, 2022 | October 1, 2010, to December 31, 2021 | April 1, 2011, to December 31, 2022 |
| Index date | Start date of first-line targeted therapy | | | |
| Lookback window | Between diagnosis date and index date (no limit to lookback period to identify diagnosis date for NSCLC, although it is expected that first-line targeted therapy should start soon after diagnosis date) | | | |
| Observation window | Index date (earliest is January 1, 2014) to October 31, 2023 (Ontario)<br>Index date (earliest is January 1, 2014) to December 31, 2023 (Alberta)<br>Index date (earliest is October 1, 2010) to September 30, 2023 (British Columbia)<br>Index date (earliest is April 1, 2011) to December 31, 2023 (Quebec, New Brunswick, Nova Scotia) | | | |
| Maximum follow-up date | Varies between jurisdictions but the latest follow-up date is December 31, 2023, for the Exactis cohort | | | |

## Study Population and Setting

## Table 4: Study Population

| Term | Criteria or definition |
|---|---|
| **Index date (and rationale)** | The index date in this study will be the first date of first-line targeted therapy (for actionable driver mutations for *ALK, EGFR, ROS1*) for patients with advanced NSCLC . This date was chosen because the objective of this study is to characterize patients who receive first-line targeted therapy and to determine the subsequent treatment regimens they undergo, including immunotherapies, chemotherapies, or additional targeted therapies. Therefore, it is pertinent for the patients in this study to enter the cohort on the first day they receive first-line targeted therapy. Although *RET*-targeted therapies are available in Canada, these drugs were not publicly funded during the current study's accrual period and therefore this study will not include such therapies. |
| **Ontario cohort** | |
| Inclusion criteria | The cohort will consist of patients with advanced NSCLC in Ontario who received first-line targeted therapy (for actionable driver mutations of *ALK, EGFR*, or *ROS1*) using afatinib, alectinib, brigatinib, crizotinib, entrectinib, gefitinib, lorlatinib, or osimertinib. This will include those who started treatment on public drug funding as well as those who started treatment through the Exceptional Access Program. Follow these steps for cohort creation:<br>• Identify patients (and their first treatment start dates) in the Ontario Drug Benefits Database who received first-line targeted therapy for advanced NSCLC.<br>• Identify patients from the Ontario Drug Benefits Database who received first-line targeted therapy (refer to Appendix 2, Table 12 for DIN list) between January 1, 2014, and October 31, 2022.<br>• Merge with OCR to obtain diagnosis date and cancer characteristics for NSCLC (*ICD-O-3* = C34) (refer to Appendix 2, Table 14 for histology codes).<br>• If there are multiple NSCLC diagnosis dates, keep the most recent diagnosis date in relation to the index date (start of earliest record of first-line targeted therapy) |

| Term | Criteria or definition |
|---|---|
| **Exclusion criteria** | 1. A non-NSCLC histology code (Appendix 2, Table 14) in the OCR.<br>2. A non-NSCLC primary cancer diagnosis within 5 years before the NSCLC primary cancer diagnosis date except, unless the diagnosis is brain cancer diagnosed within 30 days of the NSCLC primary cancer diagnosis.<br>3. Another primary cancer diagnosis between the NSCLC primary cancer diagnosis and the index date.<br>4. **Checkpoint:** Please output the number of patients within points 5 to 7 and discuss with team before moving forward with exclusions. The purpose of this checkpoint is to identify and classify patients who have had previous treatments before the index date (start of first-line targeted therapy). Those patients who received adjuvant chemotherapy can be included in the cohort; however, those who received systemic treatment with palliative intent would be excluded because this group would not receive targeted therapy as a first-line treatment.<br>5. Number of patients who had only 1 prior treatment before index date (targeted therapy start):<br>5.1. Identify the number of patients whose 1 prior treatment was adjuvant vinorelbine + platinum doublet (via NDFP indication) **[we should not exclude these patients]**<br>5.2. Identify the number of patients whose 1 prior treatment was adjuvant pemetrexed + platinum doublet. For this group, determine (via NDFP and ALR indication or intent) whether the pemetrexed + platinum doublet was metastatic or adjuvant intent. Please note that metastatic use should be flagged in NDFP, but adjuvant use was a special COVID-19 measure begun in 2020. This may require additional validation work with clinical experts and PDRP team to determine best algorithm. **[we should not exclude these patients]**<br>5.3. **Decision after the checkpoint explorations**: Include patients who received adjuvantt vinorelbine or adjuvant pemetrexed as defined by vinorelbine or pemetrex;ed in combination with platinum chemotherapy (cisplatin or carboplatin) and adjuvant surgery (within 120 days before vinorelbine treatment) or adjuvant radiation. Radiation is considered adjuvant if treatment lasts for 4 weeks or more OR if given among patients with stage I to III disease<br>6. Number of patients who had exactly 1 line of treatment before the index date, but it is not 1 of the 2 treatments listed in 5. This group should be excluded because targeted therapy would not be considered first line.<br>7. Number of patients who had more than 1 line of treatment before the index date. **This group should be excluded** because targeted therapy would not be considered first line. However, if a patient received more than 1 line of targeted therapy (i.e., 2 targeted therapies back-to-back with no record of previous systemic therapies), the patient would be included and the start date of the first targeted therapy would be used.<br>8. Invalid patient identification number<br>9. Age younger than 18 years<br>10. Invalid death date (death before index date; RPDB)<br>11. Invalid sex data (missing; RPDB)<br>12. Not living in Ontario on index date |
| Anticipated sample size | Approximately 2,000 |
| **Alberta cohort** | |
| Inclusion criteria | The cohort will include all patients in Alberta who received publicly funded first-line targeted therapy (afatinib, alectinib, brigatinib, ceritinib, crizotinib, entrectinib, gefitinib, or osimertinib) between January 1, 2014, and December 31, 2020. |

| Term | Criteria or definition |
|---|---|
| Exclusion criteria | • Invalid patient identification number<br>• Another primary cancer that is not NSCLC identified in Alberta Cancer Registry within 5 years before the primary NSCLC diagnosis<br>• Histology code unrelated to NSCLC<br>• New primary cancer diagnosed between primary NSCLC diagnosis and index date<br>• Received prior chemotherapy for advanced indication (i.e., nonadjuvant chemotherapy)<br>• Younger than 18 years at diagnosis<br>• Not referred (i.e., not in pharmacy or patient records)<br>• Invalid death date (death before index date)<br>• Not living in Alberta on index date |
| Anticipated sample size | Approximately 1,000 |
| **British Columbia cohort** | |
| Inclusion criteria | The cohort will include all patients diagnosed with NSCLC who received publicly funded first-line targeted therapy through the BC Provincial Systemic Therapy Program with the following:<br>• Diagnosis of lung cancer (*ICD-O-3* site C34.0-34.9)<br>• Received first-line targeted therapy (afatinib, alectinib, brigatinib, crizotinib, entrectinib, gefitinib, or osimertinib) between October 1, 2010, and December 31, 2021 |
| Exclusion criteria | • Histology unrelated to NSCLC<br>• Another primary cancer identified in BC Cancer Registry within 5 years before the primary NSCLC diagnosis<br>• Diagnosed with another primary cancer between primary NSCLC diagnosis and index date<br>• Received prior chemotherapy for advanced indication (i.e., nonadjuvant chemotherapy)<br>• Not living in BC at start of first-line therapy<br>• Younger than 18 years at diagnosis<br>• Diagnosis date before January 1, 2002 |
| Anticipated sample size | Approximately 2,000 |
| **Exactis cohorts** | |
| Inclusion criteria | The cohort will include all patients in Quebec, New Brunswick, and Nova Scotia who:<br>• are diagnosed with NSCLC<br>• received targeted therapy (afatinib, alectinib, brigatinib, ceritinib, crizotinib, entrectinib, gefitinib, osimertinib) between April 1, 2011, and December 31, 2022<br>OR<br>• had an aberration detected by standard-of-care molecular testing in *ALK* (fusion), *EGFR* (mutation, insertion or deletion), or *ROS1* (fusion). |
| Exclusion criteria | • More than 1 primary cancer within 5 years of index date<br>• Exclude any patients with non-NSCLC histology code<br>• For patients with stage I to III:<br>  ◦ More than 1 exposure to systemic therapy before exposure to targeted therapy in the adjuvant setting, with the adjuvant setting defined as the exposure period starting within 120 days of surgery OR after radiation.<br>  ◦ Exposure to only 1 systemic therapy other than chemotherapy (alone or in doublet) before |

| Term | Criteria or definition |
|---|---|
| | targeted therapy exposure in the adjuvant setting.<br>• For patients with stage IV:<br>◦ Any exposure to systemic therapy before targeted therapy. |
| Anticipated sample size | Approximately 140 |

ALR = Activity Level Report; *ICD-O-3* = *International Classification of Diseases for Oncology, Third Edition*; NDFP = New Drug Funding Program; NSCLC = non–small cell lung cancer; OCR = Ontario Cancer Registry; RPDB = Registered Persons Database.

## Study Variables

### Table 5: Baseline Variables for Full Cohort of Patients Who Received Targeted Therapy

| Variable | Variable definition | Variable output |
|---|---|---|
| **Age** | **Definition**: Age in years<br>**Assessment period**: Index date<br>**Database**: RPDB (Ontario), ACR (Alberta), EMRs (Exactis), BC Cancer Registry (British Columbia) | One continuous variable |
| **Sex** | **Definition**: Sex categorized as male, female, other<br>**Assessment period**: Index date<br>**Database**: RPDB (Ontario), ACR (Alberta), EMRs (Exactis), BC Cancer Registry (British Columbia) | One categorical variable with 3 levels |
| **Income quintile** | **Definition**: Neighbourhood income quintile<br>**Assessment period**: Index date<br>**Database**: RPDB (Ontario), Census Tract (Alberta) | One categorical variable with 6 levels (1 = lowest, 2, 3, 4, 5 = highest, missing) |
| **Year of NSCLC diagnosis** | **Definition**: Year of cancer diagnosis<br>**Assessment period**: Any time before index date (Alberta, Ontario, Exactis); 2002 onward (British Columbia)<br>**Database**: OCR (Ontario), ACR (Alberta), EMRs (Exactis), BC Cancer Registry (British Columbia) | One categorical variable (levels to be defined based on frequency distribution) |
| **Time from diagnosis to index** | **Definition**: Time from diagnosis date to index date in days<br>**Assessment period**: From diagnosis date to index date<br>**Database**: OCR (Ontario), EMRs (Alberta, and Exactis), BC Cancer Registry (British Columbia) | One continuous variable |
| **Stage of NSCLC at initial diagnosis** | **Definition**: Highest stage at diagnosis<br>**Assessment period**: At diagnosis date<br>**Database**: OCR (Ontario), ACR (Alberta), EMRs (Exactis), BC Cancer Registry (British Columbia) | One categorical variable with 5 levels (stage 1, stage 2, stage 3, stage 4; missing) |
| **Tumour histology** | **Definition**: Tumour histology at diagnosis<br>Refer to Appendix 2, Table 14 for grouping of *ICD-O-3* histology codes.<br>**Assessment period**: At diagnosis date<br>**Database**: OCR (Ontario), ACR (Alberta), EMR (Exactis), BC Cancer Registry (British Columbia) | One categorical variable with 4 levels (squamous cell carcinoma, adenocarcinoma, large cell carcinoma, other) |

| Variable | Variable definition | Variable output |
|---|---|---|
| **PD-L1 expression** | **Definition**: PD-L1 expression<br>**Assessment period**: Index date<br>**Database**: EMR (Exactis) | One categorical variable with 4 levels (< 1%, ≥ 1%, ≥ 50%, not specified)<br>One categorical variable with 3 levels (positive, negative, unknown)<br>Note: Not feasible for British Columbia, Ontario, and Alberta. Available for PMT Registry |
| **Prior adjuvant chemotherapy** | **Definition**: Indicator for prior adjuvant chemotherapy<br>Refer to Ontario Exclusion criteria 5 for definition of adjuvant chemotherapy.<br>Note: Keep in mind COVID-19 effect on adjuvant.<br>**Assessment period**: From diagnosis date to index date<br>**Database**: ALR, NDFP (Ontario), ACR (Alberta), EMR (Exactis), BC Cancer Pharmacy data (British Columbia) | One categorical variable with 2 levels (yes, no)<br>One date variable indicating start date of prior adjuvant chemotherapy |
| **Prior surgery for NSCLC** | **Definition**: Indicators for surgical resection of primary cancer.<br>CIHI intervention (CCI) or procedure (CCP) codes and service date received by patient before index date and after diagnosis date; specific details determined through clinical input (Ontario, British Columbia, Alberta). Refer to Appendix 2, Table 14 for diagnosis and procedure codes.<br>**Assessment period**: From diagnosis date to index date<br>**Database**: CIHI-DAD, CIHI-SDS, OCR (Ontario), BC Cancer Surgery database (BC), ACR (Alberta), EMRs (Exactis) | One categorical variable with 3 levels (yes, no, missing) |
| **Prior radiation for NSCLC (non-brain)** | **Definition**: Indicator for radiotherapy received by the patient before index date based on receipt of radiation, radiation date, and radiation location; specific details on any site or specific body site determined through clinical input (Ontario, British Columbia, Alberta)<br>**Assessment period**: From diagnosis date to index date<br>**Database**: ALR, OCR (Ontario), BC Cancer Radiotherapy database (British Columbia), ACR (Alberta), EMRs (Exactis) | One categorical variable with 3 levels (yes, no, missing) |
| **Prior radiation (for brain metastasis)** | **Definition**: Indicator radiotherapy to brain received by the patient before index date based on receipt of radiation, radiation date, and radiation location; specific details on any site or specific body site determined through clinical input (Ontario, British Columbia)<br>Algorithm:<br>• *ICD-10* diagnostic code C793 (“Secondary malignant neoplasm of brain and cerebral meninges”) in DAD and NACRS<br>• Radiation to the brain or head in ALR (body_region_grp = 'HEAD'), in DAD and NACRS (body_code from CCI code= (“A,” ”BA,” ”BB,” ”EA,” ”ER”) between dx date and index date. | One categorical variable with 3 levels (yes, no, missing) |

| Variable | Variable definition | Variable output |
|---|---|---|
| | • Exclude radiation if there was a new primary cancer of the head or face (includes nerves, skin bones), acute lymphocytic leukemia<br>• Exclude if new primary malignant or nonmalignant brain cancer diagnosis in OCR<br>**Assessment period**: From diagnosis date to index date<br>Note: Not feasible for Alberta<br>**Database**: ALR, OCR (Ontario), BC Cancer Radiotherapy database (British Columbia), EMRs (Exactis) | |
| **Initial targeted therapy** | **Definition**: Targeted therapy agent received at index date<br>Refer to Appendix 2 for DINs.<br>Refer to Appendix 2 for funding start date.<br>**Assessment period**: At index date<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One categorical variable with 8 levels (afatinib, alectinib, brigatinib, crizotinib, entrectinib, erlotinib, gefitinib, osimertinib)<br>One date variable |

ACR = Alberta Cancer Registry; ALR = Activity Level Reporting; CCI = Canadian Classification of Health Interventions; CCP = Canadian Classification of Diagnostic = Therapeutic = and Surgical Procedures; CIHI-DAD = Canadian Institute for Health Information – Discharge Abstract Database; CIHI-NACRS = Canadian Institute for Health Information – National Ambulatory Care Reporting System; EMR = electronic medical record; *ICD-O-3 = International Classification of Diseases for Oncology, Third Edition*; ICI = immune checkpoint inhibitor; NA = not applicable; NDFP = New Drug Funding Database; ODB = Ontario Drug Benefits; OHIP = Ontario Health Insurance Plan; PIN = Pharmaceutical Information Network; RPDB = Registered Persons Database.

## Table 6: Outcome Variables of Interest

| Variable | Variable definition | Variable output |
|---|---|---|
| Death date | **Definition**: Date of death for patients who died during observation period<br>**Assessment period**: Observation period<br>**Database**: RPDB (Ontario) BC Cancer Registry (British Columbia), EMRs (Exactis), ACR (Alberta) | One indicator variable (1 = died, 0 = death not observed)<br>One date variable; missing if death not observed |
| Censor date | **Definition**: Date of last follow-up for patients not observed to die during observation period.<br>Follow-up ends at the earliest of either:<br>• end of observation period (varies by province; refer to Table 3)<br>• date of last contact if patient is no longer a provincial resident<br>**Assessment period**: Observation period<br>**Database**: RPDB (Ontario), BC Cancer Registry (British Columbia), EMRs (Exactis), ACR (Alberta) | One date variable; missing if death is observed |
| Survival time | **Definition**: Time in days from index date to death or censoring<br>**Assessment period**: Observation period<br>**Database**: Constructed from death date, censor date | One continuous variable |

| Variable | Variable definition | Variable output |
|---|---|---|
| Duration of first exposure-targeted therapy | **Definition**: Each line indicates a new exposure based on drug names (i.e., exposure afatinib then gefitinib then osimertinib, which would count as 3 exposures). Time in days from index date to last dispensing date of targeted therapy.<br>**Assessment period**: Observation period<br>**Database**: Constructed from ODB, ALR (Ontario); PIN (Alberta); EMR (Exactis); BC Cancer Pharmacy database (British Columbia) | One continuous variable |
| Second exposure | **Definition**: Indicator for initiation of second exposure based on drug names<br>**Assessment period**: From end of first-line therapy to death or censoring<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One indicator variable (1 = initiated second line; 0 = no second-line therapy) |
| Start of second exposure | **Definition**: Start date for second exposure<br>Start of second exposure, defined as the first dispensing or infusion record following the end of first exposure-targeted therapy<br>**Assessment period**: From end of first exposure therapy to death or censoring<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One date variable; NA if patient did not initiate second line |
| Duration of second exposure | **Definition**: Time in days from start of second exposure (refer to previous) to last dispensing date of second exposure<br>**Assessment period**: Observation period<br>**Database**: Constructed from ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One continuous variable; NA if patient did not initiate second line |
| Class of second exposure | **Definition**: Class of second exposure<br>Classes of exposure to be confirmed in consultation with clinical advisors.<br>Proposed classes are:<br>• Platinum doublet therapy: include patients who received cisplatin or carboplatin concurrent with (dispensed on same date as) other chemotherapy, including but not limited to gemcitabine, vinorelbine, pemetrexed, paclitaxel, docetaxel, etoposide<br>• Single-agent chemotherapy includes patients who received gemcitabine, vinorelbine, pemetrexed, etoposide, paclitaxel, or docetaxel alone<br>• Other targeted therapy includes patients who received afatinib, alectinib, brigatinib, crizotinib, entrectinib, erlotinib, gefitinib, lorlatinib, osimertinib, or ceritinib<br>• Immunotherapy: Includes patients who received | One categorical variable with 5 levels; NA if patient did not initiate second line |

| Variable | Variable definition | Variable output |
|---|---|---|
| | atezolizumab, pembrolizumab, or nivolumab<br>• Other agents: Includes all other patients not classified in the proposed listed classes<br>**Database**: ALR, ODB (Ontario); PIN (Alberta); EMR (Exactis); BC Cancer Pharmacy database (British Columbia) | |
| Third-line therapy | **Definition**: Indicator for initiation of third-line therapy<br>Third-line therapy is defined as the next line of therapy started after the end of second-line therapy.<br>**Assessment period**: Observation period, following end of second line<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One indicator variable (1 = initiated third line; 0 = no third-line therapy) |
| Start of third-line therapy | **Definition**: Start date for third-line therapy<br>Start of third-line therapy defined as the first dispending record following the end of second-line therapy<br>**Assessment period**: From end of second-line therapy to death or censoring<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One date variable; missing if patient did not initiate third line |
| Duration of third-line therapy | **Definition**: Time in days from start of third-line therapy to last dispensing date of third-line therapy<br>**Assessment period**: Observation period<br>**Database**: Constructed from ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One continuous variable; NA if patient did not initiate third line |
| Class of third-line therapy | **Definition**: Class of third-line therapy<br>Classes defined in "class of second-line therapy"<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One categorical variable with 5 levels; missing if patient did not initiate third line |
| Fourth-line therapy | **Definition**: Indicator for initiation of fourth-line therapy<br>Fourth-line therapy is defined as any anticancer therapy started after the end of third-line therapy.<br>**Assessment period**: Observation period, following end of third line<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One indicator variable (1 = initiated third line; 0 = no fourth-line therapy) |
| Start of fourth-line therapy | **Definition**: Start date for fourth-line therapy<br>Start of fourth-line therapy, defined as the first dispending record following the end of third-line therapy<br>**Assessment period**: From end of third-line therapy to death or censoring<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis); BC Cancer Pharmacy database (British Columbia) | One date variable; NA if patient did not initiate fourth line |

| Variable | Variable definition | Variable output |
|---|---|---|
| Duration of fourth-line therapy | **Definition**: Time in days from start of fourth-line therapy to last dispensing date fourth-line therapy<br>**Assessment period**: Observation period<br>**Database**: Constructed from ODB (Ontario), PIN (Alberta); EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One continuous variable; NA if patient did not initiate fourth line |
| Class of fourth-line therapy | **Definition**: Class of fourth-line therapy<br>Classes defined in "class of second-line therapy"<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | One categorical variable with 5 levels; missing if patient did not initiate fourth line |
| Subsequent use of targeted therapy | **Definition**: Indicator of patients who received an additional targeted therapy (afatinib, ceritinib, alectinib, brigatinib, crizotinib, entrectinib, erlotinib, gefitinib, lorlatinib, osimertinib) that is different from the initial targeted therapy at any point during follow-up period.<br>If more than 1 additional targeted therapy identified (e.g., a patient has record of afatinib, alectinib, and brigatinib), please output variables for ALL additional targeted therapies.<br>Refer to Appendix 2 for DINs.<br>Refer to Appendix 2 for funding start dates.<br>**Assessment period**: Observation window<br>**Database**: ODB (Ontario), PIN (Alberta), EMR (Exactis), BC Cancer Pharmacy database (British Columbia) | Eleven indicator variables (1 indicator for each targeted therapy agent)<br>Eleven date variables indicating start date of subsequent targeted therapy for each additional targeted therapy |
| Subsequent use of immunotherapy | **Definition**: Indicator of whether patients received subsequent immunotherapy with atezolizumab, pembrolizumab, or nivolumab at any point during follow-up period.<br>Refer to Appendix 2 for funding start date.<br>**Assessment period**: Observation window<br>**Database**: ALR, NDFP (Ontario); BC Cancer Pharmacy database (British Columbia); PIN (Alberta); EMR (Exactis) | One categorical variable identifying type of ICI by drug name<br>One date variable indicating ICI start date |
| Subsequent use of immunotherapy post platinum doublet | **Definition**: For patients who received subsequent immunotherapy (refer to previous), identify if any of these patients received prior platinum doublet.<br>**Assessment period**: Observation window<br>**Database**: ALR, NDFP (Ontario); BC Cancer Pharmacy database (British Columbia); PIN (Alberta); EMR (Exactis) | One binary flag (0 or 1) |
| Year of immunotherapy start | **Definition**: Year of immunotherapy treatment start.<br>**Assessment period**: Observation window<br>**Database**: ALR, NDFP (Ontario); PIN (Alberta); BC Cancer Pharmacy database (British Columbia); EMRs (Exactis) | One categorical variable with multiple levels |
| Subsequent chemotherapy | **Definition**: Indicator of patients who received subsequent chemotherapy for advanced or metastatic NSCLC in any line. | One binary variable indicating the presence of a subsequent chemotherapy |

| Variable | Variable definition | Variable output |
|---|---|---|
| | If more than 1 subsequent chemotherapy identified (e.g., platinum doublet and monotherapy with gemcitabine), please output variables for ALL subsequent chemotherapies.<br>Refer to Appendix 2 for funding start dates.<br>**Assessment period**: Observation window<br>**Database**: ALR, NDFP (Ontario); BC Cancer Pharmacy database (British Columbia); PIN (Alberta); EMR (Exactis) | One date variable indicating the start date of this chemotherapy |
| Subsequent chemotherapy group | **Definition**: Create the following exposure classifications for subgroup analysis:<br>• Platinum doublet (platinum backbone with cisplatin vs. carboplatin)<br>• Non-platinum component with gemcitabine, vinorelbine, pemetrexed, paclitaxel, docetaxel, others<br>• Single-agent chemotherapy (gemcitabine, vinorelbine, pemetrexed, docetaxel, others) (Note: Include paclitaxel monotherapy as part of others as it is rarely used unless it is in combination with platinum).<br>**Assessment period**: Observation window<br>**Database**: ALR, NDFP (Ontario); BC Cancer Pharmacy database (British Columbia); PIN (Alberta); EMR (Exactis) | One categorical variable indicating the presence of a subsequent chemotherapy for each of instance of subsequence chemotherapy group |
| Subsequent chemotherapy with prior platinum doublet | **Definition**: For patients who received subsequent chemotherapy (refer to previous), identify if any of these patients received prior platinum doublet.<br>**Assessment period**: Observation window<br>**Database**: ALR, NDFP (Ontario); BC Cancer Pharmacy database (British Columbia); PIN (Alberta); EMR (Exactis) | One binary flag (0 or 1) |
| Year of subsequent chemotherapy start | **Definition**: Year of subsequent chemotherapy treatment start.<br>**Assessment period**: Observation window<br>**Database**: ALR, NDFP (Ontario); PIN (Alberta); BC Cancer Pharmacy database (British Columbia); EMRs (Exactis) | One categorical variable with multiple levels |
| Subsequent miscellaneous or other medications | Create the following exposure classifications for subgroup analysis:<br>1. Miscellaneous (e.g., clinical trials including immunotherapy or other chemotherapy given as part of clinical trials).<br>2. Others (to capture anything else)<br>**Database**: ALR, NDFP (Ontario); PIN (Alberta); BC Cancer Pharmacy database (British Columbia); EMRs (Exactis) | One categorical variable indicating the presence of a subsequent miscellaneous or other drug |
| Year of subsequent miscellaneous or other medication start | **Definition**: Year of subsequent treatment start.<br>**Assessment period**: Observation window<br>**Database**: ALR, NDFP (Ontario); PIN (Alberta); BC Cancer Pharmacy database (British Columbia); EMRs (Exactis) | One categorical variable with multiple levels |

| Variable | Variable definition | Variable output |
|---|---|---|
| Mean number of years between index date and subsequent line of immunotherapy treatment | **Definition**: Mean years between the date of first targeted therapy in each jurisdiction and the date of first third-line immunotherapy or chemotherapy.<br>**Assessment period**: Observation window<br>**Database**: ALR, NDFP (Ontario); BC Cancer Pharmacy database (British Columbia); EMR (Alberta, Exactis) | One continuous variable |

ACR = Alberta Cancer Registry; ALR = Activity Level Reporting; CIHI-DAD = Canadian Institute for Health Information – Discharge Abstract Database; CIHI-NACRS = Canadian Institute for Health Information – National Ambulatory Care Reporting System; EMR = electronic medical record; *ICD-10* = *International Classification of Diseases, Tenth Edition*; ICI = immune checkpoint inhibitor; NA = not applicable; NDFP = New Drug Funding Database; ODB = Ontario Drug Benefits; OHIP = Ontario Health Insurance Plan; PIN = Pharmaceutical Information Network; RPDB = Registered Persons Database.

## Data Analysis

### Table 7: Descriptive Analyses

| Descriptive measure | Details |
|---|---|
| Exposure | Treatment with publicly funded first-line targeted therapy |
| Measures of interest | 1. The numbers and proportions of patients with advanced NSCLC receiving different classes of anticancer therapies at any point after first-line use of targeted therapy. Refer to Appendix 1.<br>2. Sequencing of therapies after first-line use of targeted therapy.<br>We will summarize treatment progression and sequencing in a Sankey diagram (refer to sample in Appendix 1). To account for censoring at the end of the follow-up period, the progression of patients through lines of therapy will be presented 2 ways: with censoring as a separate state in the Sankey diagram and with the frequency distributions weighed using the inverse probability of censoring<br>Time to initiation of subsequent line of therapy will be estimated using competing risk analysis.<br>3. Utilization of ICI<br>We will characterize utilization of ICI at any point after first-line use of targeted therapy. Additional subgroup analysis for the patients treated with ICIs patients is described subsequently. |
| Analytic software | SAS 9.4 (Ontario, British Columbia)<br>R (v.4.2.2 in Alberta and v.4.3.0 for Exactis) |
| Sampling and weighting | NA |
| Missing data methods | NA |
| Bias due to loss to follow-up | Our cohort will be subject to uninformative censoring at the end of the follow-up period. Survival analysis methods (competing risk analysis and KM survival) that account for censoring will be used in the analysis of time-to-event data. We will account for censoring in our analysis of treatment sequencing in 2 ways: by treating censoring as a separate health state and by weighting observed patients (i.e., study sample) by the inverse probability of censoring |
| Subgroup analyses | 1. Stratification by time period<br>Over the course of the study period, new targeted therapies and later-line therapies, including ICI, will become available for advanced NSCLC. Sample size permitting, we will stratify analyses by treatment period to explore changes in treatment |

| Descriptive measure | Details |
|---|---|
| | distributions and sequencing over time. Relevant time periods will be informed by treatment funding dates (can be found in Appendix 2, Table 11) in consultation with clinical experts.<br>2. Nested cohort of ICI users<br>We will conduct a separate analysis for the subgroup of patients who received ICI at any point after first-line targeted therapy.<br>Start date of ICI therapy will be used a secondary index date for this subgroup analysis. Age, time since diagnosis, and survival and censoring time will be recalculated relative to this secondary index date. Additional variables will be constructed to describe the time since start of first-line therapy (i.e., time from index date to initiation of ICI), the line in which ICI therapy was delivered, and indicators for prior treatment by class (platinum doublet, chemotherapy monotherapy, other targeted therapy, other).<br>The characteristics of patients receiving ICI will be summarized in a table (refer to Appendix 1, Table 10). Sample size permitting, we will summarize prior treatment pathways in a Sankey diagram. |

ICI = immune checkpoint inhibitor; KM = Kaplan-Meier; NA = not applicable; NSCLC = non–small cell lung cancer.

## Data Sources

### Table 8: Data Sources by Province

| Province and data type | Data sources |
|---|---|
| **Ontario** | |
| Cohort creation | • **ODB database**: All records of publicly funded medications in Ontario<br>• **ALR database**: Records of visits to oncology centres in Ontario<br>• **OCR**: Records of cancer diagnoses<br>• **RPDB**: Demographics data |
| Clinical and demographic characteristics | • **CIHI-DAD**: All records of procedures and diagnoses that occur in an inpatient setting<br>• **CIHI-SDS**: Records of same day surgeries<br>• **OHIP**: All records of procedures and diagnoses that occur in an outpatient setting<br>• **NDFP**: All records of new and expensive injectable cancer drugs administered in hospital settings in Ontario<br>• **OCR**<br>• **ODB**<br>• **ALR**<br>• **RPDB** |
| Outcomes | • **CIHI-NACRS database**: All records of procedures and diagnoses that occur in the ambulatory setting<br>• **CIHI-DAD**<br>• **OHIP**<br>• **CIHI-SDS**<br>• **ODB**<br>• **RPDB** |

| Province and data type | Data sources |
|---|---|
| **Alberta** | |
| Cohort creation | **PIN database**: All records of prescription medications dispensed in Alberta for all payers |
| Clinical and demographic characteristics and outcomes | **Alberta Cancer Registry**: Records of patient demographics, cancer diagnosis, and mortality |
| **British Columbia** | |
| Cohort creation | • **BC Provincial Systemic Therapy Program (Pharmacy database)**: Pharmacy dispensing records for all publicly funded systemic therapies<br>• **BC Cancer Registry**: Records of patient demographics, cancer diagnosis, and mortality |
| Clinical and demographic characteristics) and outcomes | • **BC Cancer Registry**: Records of patient demographics, cancer diagnosis, and mortality<br>• **BC Provincial Systemic Therapy Program (Pharmacy database)**: Pharmacy dispensing records for all publicly funded systemic therapies<br>• **BC Cancer Radiotherapy treatment data**: All records of radiotherapy treatment (planning and delivery) in British Columbia<br>• **BC Cancer Surgery database**: Records of all surgical procedures received by BC Cancer patients from 6 months before diagnosis onward |
| **Quebec, New Brunswick, and Nova Scotia** | |
| Cohort creation clinical and demographic characteristics | **PMT Registry, Exactis Innovation**: Data collected in the PMT Registry abstracted from electronic medical records of patients enrolled in the PMT initiative |

ALR = Activity Level Report Reporting; CIHI-DAD = Canadian Institute for Health Information – Discharge Abstract Database; CIHI-SDS = Canadian Institute for Health Information – Same Day Surgery; NACRS = National Ambulatory Care Reporting System; NDFP = New Drug Funding Program; OCR = Ontario Cancer Registry; ODB = Ontario Drug Benefits; OHIP = Ontario Health Insurance Plan; PIN = Pharmaceutical Information Network; PMT = Personalize My Treatment; RPDB = Registered Persons Database.

### Study Size, Precision, and Feasibility

A power and sample size calculation is not required for this utilization study; however, the results of this study will inform the feasibility of a comparative effectiveness analysis of ICI versus single-agent chemotherapy in the subsequent-line setting for patients with advanced NSCLC bearing actionable driver mutations who received first-line targeted therapy.

## Limitations

- **Ontario:** Mutation-specific targeted therapies are oral medications, which can only be captured for patients on public drug funding programs. Therefore, we may underreport the number of patients who receive these medications.
- **Exactis cohort:** The Quebec cohort will comprise individuals in a voluntary registry and therefore generalizability to broader populations may be limited.

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# Appendix 1: Mock Tables and Figures

Note that this appendix has not been copy-edited.

Results summary templates (e.g., mock tables) to be included with initial protocol submission or at agreed-upon later date (e.g., upon completion of statistical analysis plan).

## Table 9: Cohort Characteristics on Index Date for Patients Who Received Targeted Therapy (Full Cohort)

| Baseline Characteristics | Total | ON | AB | BC | Exactis |
|---|---|---|---|---|---|
| Age | | | | | |
| Sex | | | | | |
| Income Quintile | | | | | |
| Year of NSCLC Diagnosis | | | | | |
| Time from Diagnosis to Index Date (in days) | | | | | |
| Stage of NSCLC at Initial Diagnosis | | | | | |
| Tumour Histology | | | | | |
| PD-L1 expression:<br>Positive<br>Negative<br>Unknown | | x | x | x | |
| PD-L1 expression:<br>< 1%<br>1%+<br>50%+ | | x | x | x | |
| Prior Adjuvant Chemotherapy | | | | | |
| Year of Starting Prior Adjuvant Chemotherapy (will categorize years as applicable when data are available) | | | | | |
| Prior Surgery for NSCLC | | | | | |
| Prior Radiation for NSCLC | | | | | |
| Prior Radiation to Brain | | | x | | |
| Targeted Therapy: | | | | | |
| afatinib | | | | | |
| alectinib | | | | | |
| brigatinib | | | | | |

| Baseline Characteristics | Total | ON | AB | BC | Exactis |
|---|---|---|---|---|---|
| crizotinib | | | | | |
| entrectinib | | | | | |
| gefitinib | | | | | |
| lorlatinib | | | | | |
| osimertinib | | | | | |
| Year of Starting Targeted Therapy (will categorize years as applicable when data are available) | | | | | |

## Table 10: Cohort Characteristics at the Start of Subsequent-Line Single-Agent ICI or Chemotherapy

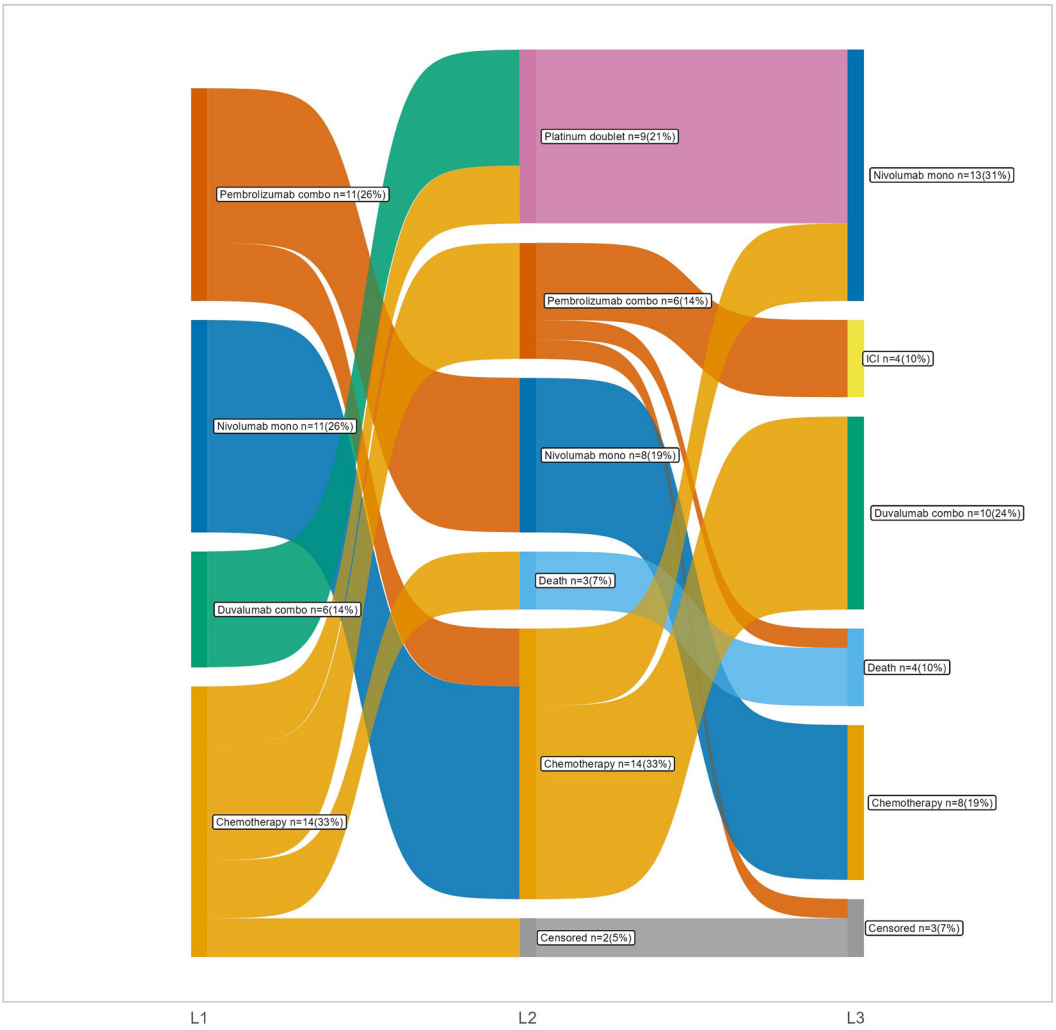
| | Subsequent-line single-agent chemotherapy | | | | | Subsequent-line single-agent ICI (any subsequent line of ICI) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Characteristic of interest | Total | ON | AB | BC | Exactis | Total | ON | AB | BC | Exactis |
| Age | | | | | | | | | | |
| Sex | | | | | | | | | | |
| Income Quintile | | | | | | | | | | |
| Mean Number of Years Between First- and Third-Line Treatment | | | | | | | | | | |
| Year of NSCLC Diagnosis | | | | | | | | | | |
| Stage of NSCLC at Initial Diagnosis | | | | | | | | | | |
| Tumour Histology | | | | | | | | | | |
| PD-L1 expression:<br>Positive<br>Negative<br>Unknown | | x | x | exploratory | | | x | x | exploratory | |
| PD-L1 expression:<br>< 1%<br>1%+<br>50%+ | | x | x | exploratory | | | x | x | exploratory | |
| Prior Surgery for NSCLC | | | | | | | | | | |
| Prior Radiation for NSCLC | | | | | | | | | | |
| Targeted Therapy: | | | | | | | | | | |
| afatinib | | | | | | | | | | |

| Characteristic of interest | Subsequent-line single-agent chemotherapy | | | | | Subsequent-line single-agent ICI (any subsequent line of ICI) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total | ON | AB | BC | Exactis | Total | ON | AB | BC | Exactis |
| alectinib | | | | | | | | | | |
| brigatinib | | | | | | | | | | |
| crizotinib | | | | | | | | | | |
| entrectinib | | | | | | | | | | |
| gefitinib | | | | | | | | | | |
| lorlatinib | | | | | | | | | | |
| osimertinib | | | | | | | | | | |
| ceritinib | | | | | | | | | | |
| others | | | | | | | | | | |
| Year of Targeted Therapy Start (dates TBD when data available) | | | | | | | | | | |
| Prior Radiation to Brain | | | | | | | | | | |
| Subsequent ICI drug:<br>Atezolizumab<br>Pembrolizumab<br>Nivolumab | N/A | N/A | N/A | N/A | N/A | | | | | |
| Year of Subsequent ICI Start:<br>2017<br>2018<br>2019<br>2020<br>2021<br>2022 | N/A | N/A | N/A | N/A | N/A | | | | | |
| Subsequent single-agent Chemotherapy type:<br>Pemetrexed<br>Docetaxel<br>Paclitaxel<br>Vinorelbine<br>Gemcitabine<br>Etoposide | | | | | | N/A | N/A | N/A | N/A | N/A |
| Year of subsequent single-agent Chemotherapy Start:<br>2017<br>2018 | | | | | | N/A | N/A | N/A | N/A | N/A |

| Characteristic of interest | Subsequent-line single-agent chemotherapy | | | | | Subsequent-line single-agent ICI (any subsequent line of ICI) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Total | ON | AB | BC | Exactis | Total | ON | AB | BC | Exactis |
| 2019 | | | | | | | | | | |
| 2020 | | | | | | | | | | |
| 2021 | | | | | | | | | | |
| 2022 | | | | | | | | | | |

## Figure 2: Sankey Diagram Depicting Treatment Sequencing (Sample Figure Only)

Sankey diagram depicting treatment sequencing



# Appendix 2: Additional and Supporting Information

Note that this appendix has not been copy-edited.

## Table 11: Summary of Funding Dates

| Treatment | Ontario | Alberta | British Columbia | Quebec | New Brunswick | Nova Scotia |
|---|---|---|---|---|---|---|
| **Targeted therapies** | | | | | | |
| ***ALK* targeted therapies** | | | | | | |
| Alectinib | 17-Apr-19 | 01- Mar-19 | 01-May-19 | 01-Feb-19 | 31-Jan-19 | 01-Dec-23 |
| Lorlatinib | 17-Jul-23 | 01-Jun-23 | Not funded | 06-07-23 | 23-Oct-23 | 01-Sep-23 |
| Brigatinib | 10-Feb-22 | 1-Feb-22 | 01-Jun-22 | Not funded | 29-April-22 | 01-Dec-23 |
| Ceritinib | 11-Oct-18 | 30-Oct-18 | 01-Sep-18 | Not funded in first line | Not funded in first line | 01-Dec-23 |
| Crizotinib | 04-Dec-15 | Not found | 01-Dec-15 | 03-Feb-14 | 30-Jan-15 | 01-Dec-23 |
| ***EGFR* targeted therapies** | | | | | | |
| Erlotinib | Not funded in first line | 01-Nov-17 | Not funded in first line | Not funded in first line | Not funded in first line | 01-Dec-23 |
| Gefitinib | 16-Sep-11 | 01-Apr-20 | 01-Oct-10 | 23-Nov-11 | Not funded in first line | Not found |
| Afatinib | 19-Aug-14 | 01-Sep-14 | 01-Oct-14 | 04-May-16 | 03-Feb-10 | Not found |
| Osimertinib | 10-Jan-20 | 01-Nov-18 | 01-Oct-18 | 18-Dec-19 | 19-Mar-20 | Not found |
| ***ROS1* targeted therapies** | | | | | | |
| Crizotinib | 04-Dec-15 | 01-Dec-15 | 01-Jul-20 | 29-Apr-20 | 16-Jul-20 | 01-Jan-21 |
| Entrectinib | 23-Dec-21 | 01-Nov-21 | 01-Apr-22 | 18-Aug-21 | 14-Oct-21 | 21-Nov-21 |
| **RET-targeted therapies** | | | | | | |
| Selpercatinib | 31-Jul-23 | 01-Aug-23 | 01-Sep-23 | 25-May-23 | 18-Sep-23 | Not found |
| Pralsetinib | Not funded | Not funded | Not funded | 25-May-23 | Not funded | Not found |
| **Subsequent-line ICIs** | | | | | | |
| Atezolizumab | 06-Dec-19 | 01-Oct-19 | 01-Nov-19 | 01-Feb-19 | Not found | Not found |
| Pembrolizumab | 17-Jan-18 | 01-Feb-18 | 01-Feb-18 | 15-Nov-17 | Not found | Not found |
| Nivolumab | 21-Mar-17 | 01-Apr-17 | 01-Mar-17 | 15-Mar-17 | Not found | Not found |

## Table 12: List of DINs for Targeted Therapies in Advanced or Metastatic NSCLC

| Drug Name | Inhibitor type | Funding notes | DIN |
|---|---|---|---|
| Crizotinib | ALK, ROS-1 (off label) | EAP | 02384256 |
| | | | 02384264 |
| Alectinib | ALK | EAP | 02458136 |
| Brigatinib | ALK | EAP | 02479206 |
| | | | 02479214 |
| | | | 02479222 |
| | | | 02479230 |
| Lorlatinib | ALK | EAP | 02485966 |
| | | | 02485974 |
| Ceritinib | ALK | EAP | 02436779 |
| Osimertinib | EGFR | EAP | 02456222 |
| | | EAP (case-by-case) | 02456214 |
| Afatinib | EGFR | EAP | 02415666 |
| | | | 02415674 |
| | | | 02415682 |
| Erlotinib | EGFR | ODB | 02461862 |
| | | | 02461870 |
| | | | 02461889 |
| | | | 02483912 |
| | | | 02483920 |
| | | | 02483939 |
| | | | 02454386 |
| | | | 02454394 |
| | | | 02269007 |
| | | | 02269015 |
| | | | 02269023 |
| | | | 02377691 |
| | | | 02377705 |
| | | | 02377713 |
| Gefitinib | EGFR | ODB | 02468050 |
| | | | 02248676 |
| | | | 02500663 |
| | | | 02491796 |

| Drug Name | Inhibitor type | Funding notes | DIN |
|---|---|---|---|
| | | | 02487748 |
| | | Approved, not marketed | 02533685 |
| Selpercatinib | RET | EAP - but started in Aug 2023 | 02516926 |
| | | | 02516918 |
| Entrectinib | RET, NTRK | — | 02495015 |

## Table 13: List of Immunotherapy DINs for Advanced or Metastatic NSCLC

| Drug Name | DIN |
|---|---|
| Atezolizumab | 0246299 |
| | 0249239 |
| Pembrolizumab | 0244115 |
| | 0245686 |
| Nivolumab | 0244662 |
| | 0244663 |
| | 0254141 |

## Table 14: List of *ICD-O* Codes for Advanced or Metastatic NSCLC

| ICD-O-3 Primary Tumor Site Codes | ICD-O-3 Histology Codes |
|---|---|
| C34.0-C34.9 | All histology except histology codes for small cell lung cancer (8002, 8041-8045) |
| NSCLC histology types | |
| Squamous cell carcinoma | 8051-8052, 8070-8076, 8078, 8083-8084, 8090, 8094, 8123 |
| Adenocarcinoma | 8015, 8050, 8140-8141, 8143-8145, 8147, 8190, 8201, 8211, 8250-8255, 8260, 8290, 8310, 8320, 8323, 8333, 8401, 8440, 8470-8471, 8480-8481, 8490, 8503, 8507, 8550, 8570-8572, 8574, 8576 |
| Large cell carcinoma | 8012-8014, 8021, 8034, 8082 |
| Other | 8000, 8003-8004, 8010, 8020, 8022, 8030, 8031-8033, 8035, 8046, 8120, 8200, 8230, 8240-8241, 8243-8246, 8249, 8265, 8430, 8525, 8560, 8562, 8575 |

Source: Ganti AK, Klein AB, Cotarla I, Seal B, Chou E. Update of incidence, prevalence, survival, and initial treatment in patients with non–small cell lung cancer in the US. *JAMA Oncol*. Published online October 21, 2021. doi:10.1001/jamaoncol.2021.4932

## Table 15: Diagnosis Codes for Lung Cancer for the Prior Surgery Variable

| ICD-10 CA CODE | Long description |
|---|---|
| C00 to C97 | All malignant 'C' diagnosis codes |
| D022 | Carcinoma in situ of bronchus and lung |
| D023 | Carcinoma in situ of other parts of respiratory system |
| D024 | Carcinoma in situ of respiratory system, unspecified |
| D143 | Benign neoplasm of bronchus and lung |
| D144 | Benign neoplasm of respiratory system, unspecified |
| D150 | Benign neoplasm of thymus |
| D152 | Benign neoplasm of mediastinum |
| D157 | Benign neoplasms of other specified intrathoracic organs |
| D159 | Benign neoplasm of intrathoracic organ, unspecified |
| D190 | Benign neoplasm of mesothelial tissue of pleura |
| D380 | Neoplasm of uncertain or unknown behaviour of larynx |
| D381 | Neoplasm of uncertain or unknown behaviour of trachea, bronchus and lung |
| D382 | Neoplasm of uncertain or unknown behaviour of pleura |
| D383 | Neoplasm of uncertain or unknown behaviour of mediastinum |
| D384 | Neoplasm of uncertain or unknown behaviour of thymus |
| D385 | Neoplasm of uncertain or unknown behaviour of other respiratory organs |
| D386 | Neoplasm of uncertain or unknown behaviour of respiratory organ, unspecified |
| D001 | Carcinoma in situ of esophagus |
| D130 | Benign neoplasm of esophagus |
| D142 | Benign neoplasm of trachea |
| D167 | Benign neoplasm of ribs, sternum and clavicle |
| D038 | Melanoma in situ of other sites |
| D039 | Melanoma in situ, unspecified |
| D048 | Carcinoma in situ of skin of other sites |
| D049 | Carcinoma in situ of skin, unspecified |
| D097 | Carcinoma in situ of other specified sites |
| D099 | Carcinoma in situ, unspecified |
| D197 | Benign neoplasm of mesothelial tissue of other sites |
| D199 | Benign neoplasm of mesothelial tissue, unspecified |
| D367 | Benign neoplasm of other specified sites |
| D369 | Benign neoplasm of unspecified site |
| D487 | Neoplasm of uncertain or unknown behaviour of other specified sites |

| ICD-10 CA CODE | Long description |
|---|---|
| D489 | Neoplasm of uncertain or unknown behaviour, unspecified |

## Table 16: Procedure Codes for Surgical Resection for the Prior Surgery Variable

| CCI CODE | Long description | Length of stay category | Notes |
|---|---|---|---|
| 1GJ87LA | Excision partial, trachea open approach [e.g., transcervical, collar incision] with simple apposition [anastomosis] | Lung - Other | — |
| 1GJ87LANR | Excision partial, trachea open approach with stent implant with simple apposition [anastomosis] | Lung - Other | — |
| 1GJ87LANRA | Excision partial, trachea open approach with stent implant using autograft | Lung - Other | — |
| 1GJ87LANRE | Excision partial, trachea open approach and stent implant using local flap (e.g., omental wrap, pericardial patch) | Lung - Other | — |
| 1GJ87LAXXA | Excision partial, trachea open approach [e.g., transcervical, collar incision] using autograft | Lung - Other | — |
| 1GJ87LAXXE | Excision partial, trachea open approach [e.g., transcervical, collar incision] using local flap (e.g., omental wrap, pericardial patch) | Lung - Other | — |
| 1GJ87QB | Excision partial, trachea open thoracic approach [e.g., mediastinal, posterolateral thoracotomy] with simple apposition [anastomosis] | Lung - Other | — |
| 1GJ87QBNR | Excision partial, trachea open thoracic approach with stent implant with simple apposition [anastomosis] | Lung - Other | — |
| 1GJ87QBNRA | Excision partial, trachea open thoracic approach with stent implant using autograft | Lung - Other | — |
| 1GJ87QBNRE | Excision partial, trachea open thoracic approach with stent implant using local flap (e.g., omental wrap, pericardial patch) | Lung - Other | — |
| 1GJ87QBXXA | Excision partial, trachea open thoracic approach [e.g., mediastinal, posterolateral thoracotomy] using autograft | Lung - Other | — |
| 1GJ87QBXXE | Excision partial, trachea open thoracic approach [e.g., mediastinal, posterolateral thoracotomy] using local flap (e.g., omental wrap, pericardial patch) | Lung - Other | — |
| 1GM87DA | Excision partial, bronchus NEC using endoscopic (percutaneous) approach | Lung - Other | — |
| 1GM87LA | Excision partial, bronchus NEC using open approach | Lung - Other | — |
| 1GR87DA | Excision partial, lobe of lung using endoscopic approach [VATS] | Lung - Other | — |

| CCI CODE | Long description | Length of stay category | Notes |
|---|---|---|---|
| 1GR87NW | Excision partial, lobe of lung using intrapericardial [transpericardial] approach | Lung - Other | — |
| 1GR87QB | Excision partial, lobe of lung using open thoracic approach | Lung - Other | — |
| 1GT87DA | Excision partial, lung NEC using endoscopic approach [VATS] | Lung - Other | — |
| 1GT87NW | Excision partial, lung NEC using intrapericardial [transpericardial] approach | Lung - Other | — |
| 1GT87QB | Excision partial, lung NEC using open thoracic approach | Lung - Other | — |
| 1ME87DA | Excision partial, lymph node(s), mediastinal using endoscopic approach | Lung - Other | Alone- diagnostic procedure (not curative)<br>With other resection code- ignore since resection code Is enough to determine curative intent |
| 1ME87LA | Excision partial, lymph node(s), mediastinal using open approach | Lung - Other | Alone- diagnostic procedure (not curative)<br>With other resection code- ignore since resection code Is enough to determine curative intent |
| 1MF87DA | Excision partial, lymph node(s), intrathoracic NEC using endoscopic approach | Lung - Other | — |
| 1MF87LA | Excision partial, lymph node(s), intrathoracic NEC using open approach | Lung - Other | — |
| 1MN87DA | Excision partial, lymphatic vessels of thoracic region no tissue used Endoscopic approach | Lung - Other | — |
| 1GN92LA | Excision radical with reconstruction, carina using open approach | Lung - Other | — |
| 1GR91NW | Excision radical, lobe of lung open intrapericardial [transpericardial] approach with simple closure | Lobectomy | — |
| 1GR91NWXXA | Excision radical, lobe of lung open intrapericardial [transpericardial] approach using autograft [pericardium] | Lobectomy | — |
| 1GR91NWXXF | Excision radical, lobe of lung open intrapericardial [transpericardial] approach using free flap | Lobectomy | — |
| 1GR91NWXXG | Excision radical, lobe of lung open intrapericardial [transpericardial] approach using distant pedicled flap | Lobectomy | — |
| 1GR91NWXXL | Excision radical, lobe of lung open intrapericardial [transpericardial] approach using xenograft | Lobectomy | — |

| CCI CODE | Long description | Length of stay category | Notes |
|---|---|---|---|
| 1GR91NWXXN | Excision radical, lobe of lung open intrapericardial [transpericardial] approach using synthetic material | Lobectomy | — |
| 1GR91NWXXQ | Excision radical, lobe of lung open intrapericardial [transpericardial] approach using combined sources of tissue | Lobectomy | — |
| 1GR91QB | Excision radical, lobe of lung open thoracic approach with simple closure | Lobectomy | — |
| 1GR91QBXXA | Excision radical, lobe of lung open thoracic approach using autograft [pericardium] | Lobectomy | — |
| 1GR91QBXXF | Excision radical, lobe of lung open thoracic approach using free flap | Lobectomy | — |
| 1GR91QBXXG | Excision radical, lobe of lung open thoracic approach using distant pedicled flap | Lobectomy | — |
| 1GR91QBXXN | Excision radical, lobe of lung open thoracic approach using synthetic material | Lobectomy | — |
| 1GR91QBXXQ | Excision radical, lobe of lung open thoracic approach using combined sources of tissue | Lobectomy | — |
| 1GT91NW | Excision radical, lung NEC using simple closure open intrapericardial [transpericardial] approach | Pneumonectomy | — |
| 1GT91NWXXF | Excision radical, lung NEC using free flap open intrapericardial [transpericardial] approach | Pneumonectomy | — |
| 1GT91NWXXG | Excision radical, lung NEC using distant pedicled flap open intrapericardial [transpericardial] approach | Pneumonectomy | — |
| 1GT91NWXXN | Excision radical, lung NEC using synthetic material open intrapericardial [transpericardial] approach | Pneumonectomy | — |
| 1GT91NWXXQ | Excision radical, lung NEC using combined sources of tissue open intrapericardial [transpericardial] approach | Pneumonectomy | — |
| 1GT91QB | Excision radical, lung NEC with simple closure open thoracic approach | Pneumonectomy | — |
| 1GT91QBXXF | Excision radical, lung NEC using free flap open thoracic approach | Pneumonectomy | — |
| 1GT91QBXXG | Excision radical, lung NEC using distant pedicled flap open thoracic approach | Pneumonectomy | — |
| 1GT91QBXXN | Excision radical, lung NEC using synthetic material open thoracic approach | Pneumonectomy | — |
| 1GT91QBXXQ | Excision radical, lung NEC using combined sources of tissue open thoracic approach | Pneumonectomy | — |
| 1GR89DA | Excision total, lobe of lung using endoscopic approach [VATS] | Lobectomy | — |

| CCI CODE | Long description | Length of stay category | Notes |
|---|---|---|---|
| 1GR89NW | Excision total, lobe of lung using intrapericardial [transpericardial] approach | Lobectomy | — |
| 1GR89QB | Excision total, lobe of lung using open thoracic approach | Lobectomy | — |
| 1GT89DA | Excision total, lung NEC using endoscopic approach [VATS] | Pneumonectomy | — |
| 1GT89NW | Excision total, lung NEC using intrapericardial [trans pericardial] approach | Pneumonectomy | — |
| 1GT89QB | Excision total, lung NEC using open thoracic approach | Pneumonectomy | — |
| 1ME89DA | Excision total, lymph node(s), mediastinal using endoscopic approach | Lung - Other | Alone- diagnostic procedure (not curative)<br>With other resection code- ignore since resection code Is enough to determine curative intent |
| 1ME89LA | Excision total, lymph node(s), mediastinal using open approach | Lung - Other | Alone- diagnostic procedure (not curative)<br>With other resection code- ignore since resection code Is enough to determine curative intent |

## Administrative Codes to Identify Brain Metastasis for Prior Brain Radiation Variable

### Diagnostic code C793 (*ICD10* code): Secondary Malignant Neoplasm of Brain and Cerebral Meninges

Procedure and diagnostic codes were obtained from DAD (Discharge Abstract Database; includes data on all procures performed in-hospital during an inpatient visit) and NACRS (National Ambulatory Care Reporting System) includes data on all procedures performed in-hospital during an outpatient visit.

For more information on CoLab and its work visit **colab.cadth.ca**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