COMPARATIVE CLINICAL AND COST-EFFECTIVENESS ANALYSIS OF FIRST- AND SECOND-LINE THERAPIES FOR THE TREATMENT OF ADVANCED OR METASTATIC NON-SMALL-CELL LUNG CANCER IN ONTARIO, CANADA

by

Yong-Jin Kim

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Examining Committee Membership

The following served on the Examining Committee for this thesis. The decision of the Examining Committee is by majority vote.

External Examiner	Natasha Leighl Professor, Dalla Lana School of Public Health, Institute of Health Policy, Management and Evaluation University of Toronto
Supervisor	Susan Horton Professor, School of Public Health and Health Systems University of Waterloo
Internal Members	Mark Oremus Associate Professor, School of Public Health and Health Systems University of Waterloo Helen Chen Professor of Practice, Associate Director, Professional Practice Centre for Health Systems, Department of Statistics and Actuarial Science; Department of Computer Science; and School of Public Health and Health Systems University of Waterloo
Internal/External Examiner	Thomas McFarlane Clinical Lecturer, School of Pharmacy University of Waterloo

Author's Declaration

This thesis consists of material all of which I authored or co-authored: see Statement of Contributions included in the thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be electronically available to the public.

Statement of Contributions

The manuscripts and studies presented in this thesis, including three that have been published in peer-reviewed academic journals are the work of Yong-Jin Kim, in collaboration with his co-authors and committee members. The authorship for each thesis chapter (and the corresponding manuscripts thereof) is shown below.

Chapter	Description	Reference	Status
3.0	Study 1	Kim, Y. J., Oremus, M., Chen, H. H., McFarlane, T., Shah, D., & Horton, S. (2020). Real-world effectiveness of nivolumab in patients with non-small-cell lung cancer: a systemic review and meta-analysis. *Future Oncol, 16*(27), 2045-2058. doi: 10.2217/fon-2020-0248.	Published
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5.0	Study 3	Kim, Y. J., Oremus, M., Chen, H. H., McFarlane, T., Fearon, D., & Horton, S. (2021). Cost-effectiveness analysis of afatinib, erlotinib, and gefitinib as first-line treatments for EGFR mutation-positive non-small-cell lung cancer in Ontario, Canada. *Pharmacoeconomics, 39*(5), 537-548. doi: 10.1007/s40273-021-01022-9.	Published

As the lead author of the three main studies, I was responsible for the conceptualization of study design, data collection and analysis, and drafting and submitting manuscripts. My co-authors provided methodological guidance, supported data analyses, and provided feedback on draft manuscripts, with full knowledge that the publication would be included in the doctoral thesis of Yong-Jin Kim.

Abstract

Background: Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in Canada. Over the last decade, significant advancements in treatments for non-small-cell lung cancer (NSCLC) have been made. Development of novel therapies such as tyrosine kinase inhibitors (TKIs) and immunotherapies (i.e., immune checkpoint inhibitors) have offered a new paradigm for the treatment of NSCLC. While several randomized controlled trials demonstrated the efficacy of TKIs and immunotherapies, the comparative effectiveness and cost-effectiveness of these therapies in real-world setting remains unclear.

Objectives: The overall aim of this dissertation was to investigate the comparative clinical and cost-effectiveness of first- (i.e., EGFR-TKIs) and second-line therapies (i.e., immunotherapies) for the treatment of NSCLC in Ontario, Canada.

Methods: This thesis is presented as three individual studies included in Chapters 3 to 5. **Study 1** aimed to investigate the effectiveness of immunotherapies for non-small-cell lung cancer in a real-world clinical setting, as this currently remains uncertain. Systematic searches of PubMed, EMBASE and Web of Science were performed; a narrative synthesis was conducted on all included studies, with the synthesis being stratified by variables including age, sex, histology, prior lines of treatment, brain metastasis, and ECOG-PS. Separate random-effects models were used to estimate pooled median overall survival (OS) and progression-free survival (PFS) estimates. **Study 2** aimed to investigate the factors associated with treatment selection and OS for first-line EGFR-TKI therapy among patients with non-small-cell lung cancer. A retrospective cohort study of linked administrative health databases in Ontario, Canada was conducted.

To explore the factors associated with treatment selection, we conducted two separate logistic regression analyses comparing afatinib to gefitinib and erlotinib to gefitinib. Discrimination of the models was assessed with the area under the receiver operating characteristic curve. Calibration of the models was evaluated using the Hosmer Lemeshow goodness-of-fit tests. OS was assessed using the Kaplan-Meier method on the overall population and various patient subgroups. The OS was calculated from the date of diagnosis of NSCLC to death (for any reason) or the last day of patient follow-up (censored). Comparisons between groups were performed using the log rank test. Multivariable Cox proportional hazards models were used to determine adjusted hazard ratios and to evaluate the predictive factors for survival. In Study 3, a net benefit regression approach accounting for baseline covariates and propensity scores was used to estimate incremental net benefits and incremental cost-effectiveness ratios. Inverse probability of censoring weights was applied for differential censoring. Outcome measures were calculated over a 68-month period and were discounted with an annual rate of 1.5%. Sensitivity analyses were conducted to assess and characterize the uncertainties.

Results: Results from **Study 1** provided insights on the effectiveness of immunotherapies, particularly nivolumab, in real-world clinical practice. 36 studies of nivolumab were included for narrative synthesis and 11 of these studies were included for meta-analysis. Age, sex, histology and prior lines of treatment did not affect survival outcomes, while Eastern Cooperative Oncology Group Performance Status and brain metastasis were inversely associated with survival. In the meta-analysis, nivolumab was associated with 9.6 months (95% CI: 8.4–10.9) of overall survival and 2.6 months (95%

CI: 1.6–3.6) of progression-free survival. Empirical evidence suggested the real-world effectiveness of nivolumab was consistent with those observed in the clinical trials. Results from **Study 2** identified the patient characteristics influencing the treatment selection and overall survival associated with EGFR-TKI therapy. From 01 January 2010 through 31 August 2019, a total of 1,078 patients received an EGFR-TKI as first-line therapy. Of these, 1,011 patients met the eligibility criteria and were included in the study. Treatment selection and OS associated with these treatments were affected by age, sex, geographical residency, comorbidities, and different sites of metastasis. Though recent approval of osimertinib offers a potential new standard of care in the first-line setting, earlier generation TKIs remain pillars in the treatment of NSCLC therapeutic armamentarium. The findings of this study may contribute to optimizing the treatment sequencing of EGFR-TKIs to maximize clinical benefits. Results from **Study 3** investigated the comparative cost-effectiveness of EGFR-TKIs in Ontario, Canada. From 01 January 2014 and 31 August 2019, a total of 547 patients met the eligibility criteria and were included in the study. 20.1%, 23.6%, and 56.3% received afatinib, erlotinib, and gefitinib, respectively. Erlotinib was dominated by afatinib and gefitinib. Compared to gefitinib, afatinib was associated with higher effectiveness (adjusted incremental quality-adjusted life-year: 0.21), higher total costs (adjusted incremental costs: $9745), and an incremental cost-effectiveness ratio of $46,506 per quality-adjusted life-year gained. Results from the sensitivity analyses indicated the findings of the base-case analysis were robust. Our findings suggest afatinib was the most cost-effective option among the three EGFR-TKIs.

Conclusion: This dissertation investigated real-world clinical and cost-effectiveness of EGFR-TKIs and immunotherapies (nivolumab) for the first- and second-line treatments for NSCLC, and identified patient factors influencing treatment selection and overall survival associated with EGFR-TKI treatment. The findings presented throughout this thesis may contribute to the body of knowledge in regard to optimization of treatment sequences and help policymakers revise healthcare resource allocation decisions.

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List of Abbreviations

AE	Adverse Event
ALR	Activity Level Reporting
ASMR	Age Standardized Mortality Rate
AUC	Area Under the Receiver Operating Characteristic Curve
CCC	Complex Continuing Care
CCI	Charlson Comorbidity Index
CCRS	Continuing Care Reporting System
CEA	Cost Effectiveness Analysis
CEAC	Cost Effectiveness Acceptability Curve
CI	Confidence Interval
CIHI-DAD	Canadian Institute for Health Information – Discharge Abstract Database
CT	Computed Tomography
ECOG PS	Eastern Cooperative Oncology Group Performance Status
ED	Emergency Department
EGFR	Epidermal Growth Factor Receptor
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HC	Home Care
HR	Hazards Ratio
ICD-O-3	International Classification of Diseases for Oncology, Third Edition

ICER	Incremental Cost Effectiveness Ratio
ICES	Institute for Clinical Evaluative Sciences
ICI	Immune Checkpoint Inhibitor
INB	Incremental Net Benefit
IPCW	Inverse Probability of Censoring Weights
LDCT	Low-Dose Computed Tomography
LHIN	Local Health Integration Network
LTC	Long Term Care
LY	Life Year
MH	Mental Health
MRI	Magnetic Resonance imaging
NACRS	National Ambulatory Care Reporting System
NBR	Net Benefit Regression
NDFP	New Drug Funding Program
NOS	Newcastle-Ottawa Scale
NSCLC	Non-Small-Cell Lung Cancer
OCR	Ontario Cancer Registry
ODB	Ontario Drug Benefits
OHIP	Ontario Health Insurance Plan
OMHRS	Ontario Mental Health Reporting System
OR	Odds Ratio
ORR	Objective Response Rate
OS	Overall Survival

PD-1	Programmed Cell Death-1
PD-L1	Programmed Cell Death Ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjusted Life Year
RCT	Randomized Controlled Trial
RIW	Resource Intensity Weight
RPDB	Registered Persons Database
SCLC	Small-Cell Lung Cancer
TKI	Tyrosine Kinase Inhibitor
TNM	Tumor, Node, Metastasis
TRAE	Treatment Related Adverse Event
WTP	Willingness-To-Pay

Chapter 1: Introduction

Lung cancer is the most commonly diagnosed cancer and the leading cause of cancer-related deaths in Canada, with an estimated 29,800 new cases and 21,200 deaths in 2020 (Canadian Cancer Society, 2021). Non-small cell lung cancer (NSCLC) is the most common histological subtype, representing over 80% of all lung cancer cases (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2018; Cancer Care Ontario, 2018). The five-year survival rate in Canada for lung cancer is approximately 19%; despite the improved survival rate in recent years, the level of survival advancements seen in other forms of cancer (e.g., breast [88%], prostate [95%]), has yet to be seen in lung cancer (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2018; Canadian Cancer Society, 2020)

Increasing understanding of biology of cancer has led to recent advancements in personalized therapy. These advancements allow us to stratify patients by their histological and molecular subtypes to guide selection of therapeutic strategies in efforts to maximize clinical benefits and minimize treatment-related adverse events (AEs) (Korpanty et al., 2014; Naidoo, 2014). Selected patients harboring oncogenic drivers such as epidermal growth factor receptor (EGFR) are eligible to receive tyrosine kinase inhibitors (TKIs) targeted to these genetic tumor aberrations, which improve survival and prolong disease control. However, patients often acquire resistance and treatment-related adverse events with TKIs. The long-term prognosis remains poor and all patients eventually progress through the disease (Wu & Shih, 2018).

In addition to TKIs, immunotherapy (i.e., immune checkpoint inhibitors) offer a new paradigm for the treatment of NSCLC, which targets the programmed cell death-1 (PD-1) and programmed cell death ligand 1 (PD-L1) pathway. Evasion and manipulation of the immune system is a primary feature of cancers and enables tumor growth and metastasis (Beatty & Gladney, 2015; Muenst et al., 2016; Vinay

et al., 2015). Understanding the tumor evasion mechanism via the PD-1/PD-L1 signaling pathway contributed to the development of immune modulating therapies, which amplify one's own immune system to recognize and kill cancer cells.

Being able to selectively identify which patients would benefit the most from personalized therapies and immunotherapies would be of major clinical advancement in lung cancer management. With new generation of therapies emerging, investigation of the clinical benefits of these therapies, along with their cost-effectiveness is important to help select the most optimal treatment sequences for patients with NSCLC and optimize health care resource allocations. Thus, the aim of this thesis was to investigate the clinical and cost-effectiveness of first line (i.e., EGFR-TKIs) and second line (i.e., immune checkpoint inhibitors) treatments for EGFR mutation-positive NSCLC in Ontario, Canada.

1.1. Dissertation Overview

This dissertation consists of three linked manuscripts with an expanded introduction and discussion. The dissertation begins with the introduction to background information and a review of the literature in Chapter 2. The literature review focuses on the disease information, epidemiology, treatment protocols, economic burden, and cost-effectiveness of interventions associated with NSCLC. Chapters 3-5 have been written for publication and presents the three primary studies conducted for the dissertation. Chapter 3 was published in Future Oncology; Chapter 4 has been published in the Journal of Comparative Effectiveness and Research and Chapter 5 has been published in PharmacoEconomics. Chapter 6 connects all three primary studies and discusses the implications of this dissertation and provides insight on the direction of future studies. Concluding remarks are presented in Chapter 7.

1.2. Research Rationale

The first study investigated the effectiveness and safety of approved immunotherapies for the treatment of NSCLC in clinical practice through a systematic review of the literature. Among non-oncogene addicted lung cancer patients, immune checkpoint inhibitors have demonstrated superior efficacy over standard chemotherapy (e.g., docetaxel) with regards to overall survival (OS) and progression-free survival (PFS). However, evidence to date suggest the benefits of immune checkpoint inhibitors lack clinical activity in *EGFR* mutant lung cancer patients. Several observational studies reporting on the effectiveness and safety of immunotherapies for NSCLC in routine clinical practice have been published to date. We sought to collect and synthesize all empirical evidence to further understand the effectiveness of immunotherapies in the real-world and determine whether the effectiveness was comparable to what was observed in clinical trials for lung cancer patients overall (i.e, non-oncogene addicted lung cancer patients), and to synthesize results by mutation type (e.g., *KRAS*, *EGFR*, *ALK*, *HER2*), if available.

The second study investigated the patient factors that influenced treatment selection of first-line EGFR-TKIs and overall survival among *EGFR* mutation-positive NSCLC patients in routine clinical practice. Evidence-based clinical practice guidelines have been developed for prescribing these therapies to minimize adverse effects (AEs) and maximize clinical benefits. With new generations of EGFR-TKIs emerging and a number of treatment options becoming available, it is important to identify a proper agent for each patient in clinical practice to balance the risks and benefits. Leveraging the population-level data from ICES, we sought to investigate whether certain demographic or clinical factors systematically influence prescribing decisions and survival in Ontario, Canada.

The last study examined the comparative cost-effectiveness of first-line EGFR-TKIs (i.e., afatinib, erlotinib, and gefitinib) for the treatment of *EGFR* mutation-positive NSCLC. Although multiple economic evaluations have been conducted to date, the majority were model-based analyses with information derived from multiple trials to infer effectiveness using indirect treatment comparisons. The use of model analyses is associated with many limitations such as incorporation of model assumptions (e.g., Markovian assumption), restrictive inclusion and exclusion criteria, limited lengths of follow-up, extrapolation of observed survival data, and limited information on treatment-related healthcare costs. Hence, we sought to conduct a cost-effectiveness analysis using population-based, person-level claims data, which permit direct comparison of effectiveness and costs associated with TKIs for the treatment of *EGFR* mutation-positive NSCLC. Specific objectives were as follows:

Study 1: Real-world effectiveness of nivolumab in patients with non-small-cell lung cancer: a systematic review and meta-analysis

Objective: To investigate the effectiveness and safety of immune checkpoint inhibitors for the treatment of NSCLC in real-world settings.

Study 2: Factors affecting treatment selection and overall survival for first-line EGFR-TKI therapy in non-small-cell lung cancer

Objective: To examine the demographic and clinical factors influencing treatment selection and overall survival associated with first-line EGFR-TKIs for the treatment of NSCLC in Ontario, Canada.

Study 3: Cost-effectiveness analysis of afatinib, erlotinib, and gefitinib as first-line treatment for EGFR mutation-positive non-small-cell lung cancer in Ontario, Canada

Objective: To investigate the comparative cost-effectiveness of first-line EGFR-TKIs for the treatment of patients with advanced *EGFR* mutant NSCLC in Ontario, Canada.

Chapter 2: Literature Review

2.1. Categorization of Lung Cancer

2.1.1. Histologic Subtype

Lung cancer is a form of cancer whereby malignant carcinoma cells develop in the lining of the air passageway of the lungs (American Cancer Society, 2016a, 2016b) . Lung cancer can be broadly classified as NSCLC and small-cell lung cancer (SCLC). NSCLC accounts for 80%-85% of all lung cancer cases, while SCLC accounts for the remaining 10%-15% (American Cancer Society, 2016a, 2016b; Lung Cancer Alliance, 2018) .

NSCLC is the most common type of lung cancer and can be divided into three subtypes – adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma is a slow growing form of lung cancer usually found in the outer region of the lung. Adenocarcinoma is the most common form of NSCLC, accounting for 40% to 50% of all lung cancer cases (American Cancer Society, 2016a). Adenocarcinoma is more prevalent among smokers though it is also the most common form of lung cancer in non-smokers as well (American Cancer Society, 2016a; National Cancer Institute, 2018). Squamous cell carcinoma most frequently develops in the center of the chest area in the bronchi and is highly correlated with history of tobacco consumption. Squamous cell carcinoma accounts for 25% to 30% of all lung cancer cases (American Cancer Society, 2016a; National Cancer Institute, 2018). Large cell carcinoma is the least common type of NSCLC, accounting for 10% to 15% of all lung cancer cases (American Cancer Society, 2016a). Large cell carcinoma can occur anywhere in the lung and is able to grow and metastasize at a rapid rate. Staging of NSCLC is done by using the Tumor, Node, Metastasis (TNM) Classification of Malignant Tumours staging system (Table 1, Table 2).

Table 1. TNM Descriptor

T (Primary Tumor)	
T0	No evidence of tumor
Tis	Carcinoma in situ (squamous or carcinoma)
T1	Tumor ≤ 3cm
T1mi	Minimally invasive carcinoma
T1a	Tumor ≤ 1cm
T1b	Tumor > 1 but ≤ 2cm
T1c	Tumor > 2 but ≤ 3cm
T2	Tumor > 3 but ≤ 5cm or involvement of main bronchus (not carina), visceral pleura, atelectasis to hilum
T2a	Tumor > 3 but ≤ 4cm
T2b	Tumor > 4 but ≤ 5cm
T3	Tumor >5 but ≤ 7cm in greatest dimension or tumor of any size invading chest wall, pericardium, phrenic nerve or separate tumor nodules in the same lobe.
T4	Tumor > 7cm in greatest dimension or any tumor invading mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, esophagus, spine or tumor nodules in a different ipsilateral lobe
N (Regional Lymph Node)	
N0	No regional node metastasis
N1	Metastasis in ipsilateral peribronchial or hilar nodes and intrapulmonary nodes
N2	Metastasis in ipsilateral mediastinal or subcarinal nodes
N3	Metastasis in contralateral mediastinal, hilar, or ipsilateral/contralateral scalene/supraclavicular nodes
M (Distant Metastasis)	
M0	No distant metastasis
M1a	Tumor in contralateral lung or pleural/pericardial nodule or malignant pleural

T (Primary Tumor)	
M1b	Single extrathoracic metastasis
M1c	Multiple extrathoracic metastases in one or more organs

Source: AJCC Cancer Staging Manual 8th Edition, 2017

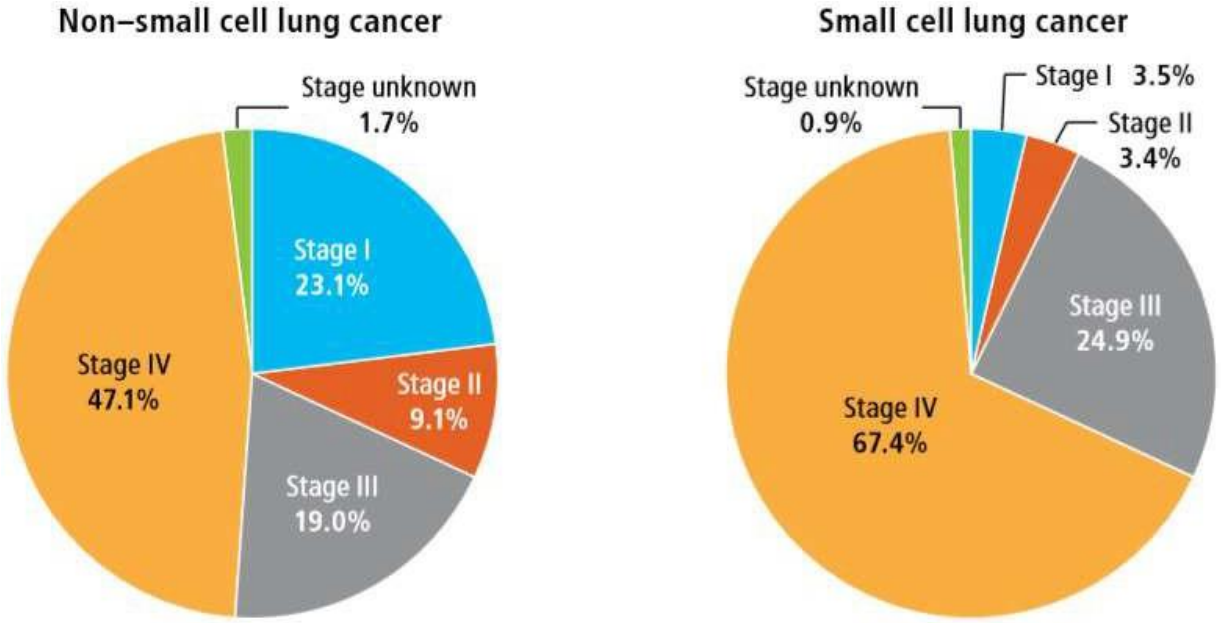
Table 2 TNM Staging for NSCLC

T/M	Subcategory	N0	N1	N2	N3
T1	T1a	IA1	IIB	IIIA	IIIB
	T1b	IA2	IIB	IIIA	IIIB
	T1c	IA3	IIB	IIIA	IIIB
T2	T2a	IB	IIB	IIIA	IIIB
	T2b	IIA	IIB	IIIA	IIIB
T3	T3	IIB	IIIA	IIIB	IIIC
T4	T4	IIIA	IIIA	IIIB	IIIC
M1	M1a	IVA	IVA	IVA	IVA
	M1b	IVA	IVA	IVA	IVA
	M1c	IVB	IVB	IVB	IVB

Source: AJCC Cancer Staging Manual 8th Edition, 2017

The stage of cancer describes how much cancer is in the body and helps to determine the magnitude of cancer and the course of treatment that is necessary. Information on staging is also used for implications in survival statistics (e.g., five-year survival rate), as well as a prognostic factor for health outcomes. The earliest stage of NSCLC is stage 0 (i.e., carcinoma in situ); other stages range from I through IV, with stage IV denoting the highest stage indicating increased metastasis. In terms of the TNM staging, higher numbers associated with each letter indicates a higher stage. Most lung cancer patients are diagnosed at stage IV (**Figure 1**).

Figure 1 Percentage distribution of lung cancer cases by stage at diagnosis

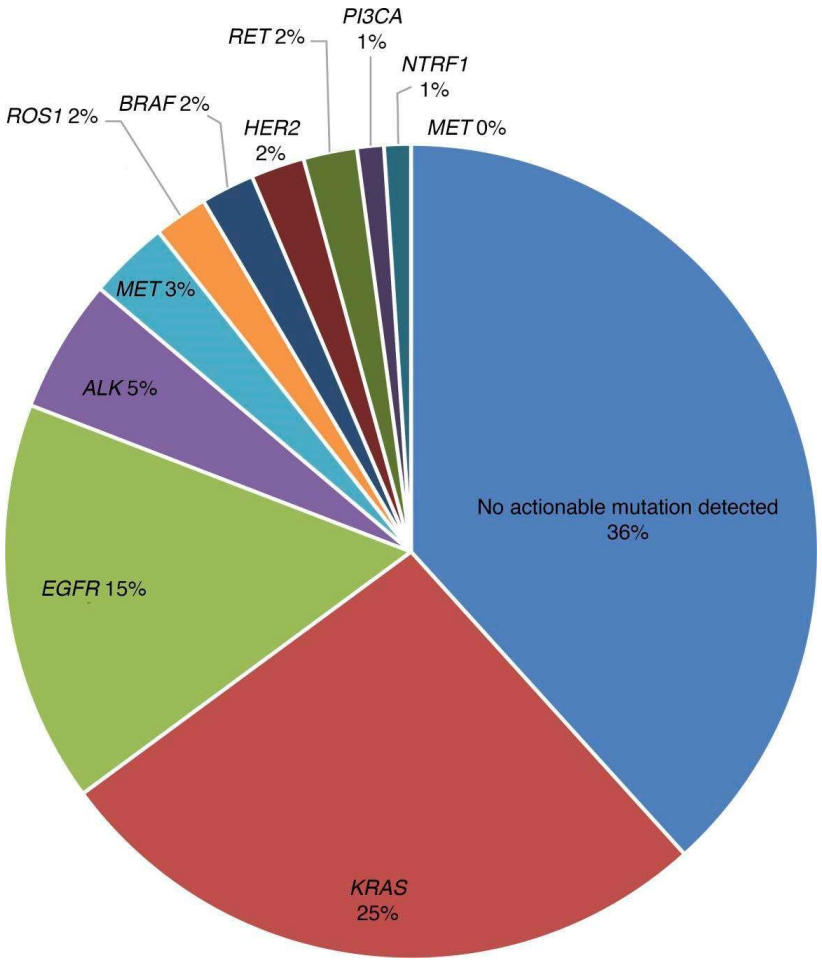


Source: Canadian Cancer Statistics: A 2018 Special Report

2.1.2. Molecular subtype

NSCLC can be further defined at the molecular level. Research into the genetics of lung cancer has led to the discovery of several gene mutations, amplifications, and rearrangements in multiple oncogenes such as *AKT1*, *ALK*, *BRAF*, *EGFR*, *HER2*, *KRAS*, *MEK1*, *MET*, *NRAS*, *PIK3CA*, *RET*, and *ROS1* (El-Telbany & Ma, 2012; Zhu et al., 2017). Cancer develop as a result of the accumulation of these genomic alterations, which results in cell growth, proliferation, resistance to apoptosis, and eventually tumorigenesis – such mutations are called "driver mutations" (Pakkala & Ramalingam, 2018; Zhu et al., 2017). Mutations are found in all histological types of lung cancer and up to 50% of NSCLC patients harbor a driver mutation (Pakkala & Ramalingam, 2018). The frequency of driver mutations is presented in Figure 2. The incidence and prevalence of driver mutations in non-small-cell lung cancer varies by countries and ethnicities (Dearden et al, 2013; Midha et al, 2015).

Figure 2 Frequency of driver mutations in NSCLC



Source: Pakkala & Ramalingam, 2018

2.2. Epidemiology

2.2.1. Incidence

Lung cancer is the leading cause of cancer-related mortality in the province of Ontario, Canada and worldwide. Approximately 29,800 new cases of lung cancer were diagnosed in Canada in 2020, the equivalent of 81 lung cancers diagnosed per day (Canadian Cancer Society, 2020). Lung cancer is the second most common cancer diagnosis for each sex, behind prostate cancer for men and breast cancer for women (Canadian Cancer Society, 2020). In 2020, approximately 15,000 men were diagnosed with lung cancer and 11,000 died from it, while 14,800 women were diagnosed and 10,200 died

(Canadian Cancer Society, 2020). The incidence rate is higher for males than females, with age-standardized incidence rates of 76.5 and 65.3 per 100,000 persons, respectively (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2018).

Recent trends suggest incidence rates have declined for both sexes. Incidence rates for men in Canada have declined since 1983 (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017), in conjunction with declines in tobacco consumption following a rise in awareness of the risks of tobacco smoking and the implementation of governmental tobacco control measures. The incidence rates have decreased more for men than women due to differences in smoking uptake and cessation. Among females, incidence rates rose until 2006 and levelled off thereafter (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2018).

2.2.2. Mortality

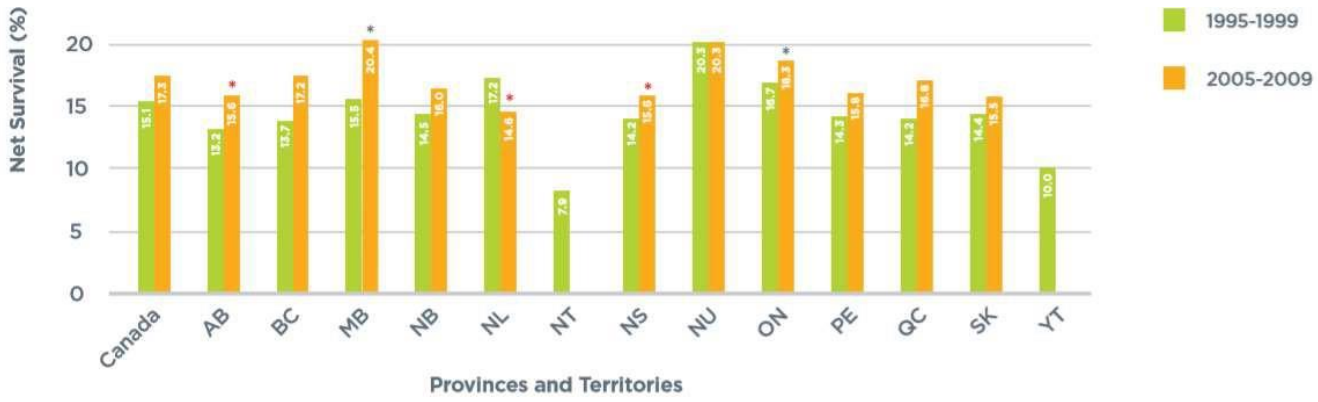
On average, 58 Canadians die from lung cancer every day. Mortality rate is higher for males than females, with age-standardized mortality rates (ASMR) of 59.4 and 45.3 per 100,000 persons, respectively (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2018). Among males, the age-standardized mortality rate began to level off in the late 1980s and saw a gradual decline from 1989 onwards (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017).

Among females, the ASMR continued to increase until 2000 and gradually decreased moving forward (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017). Decreases in mortality rates for both sexes are largely due to reduced tobacco use, which began in the late 1950s for men and mid-1970s for women (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017).

2.2.3. Survival

The five-year survival rate in Canada for lung cancer is 19% (Canadian Cancer Society, 2020). Although recent trends suggest the five-year survival rate has improved gradually over the years (Figure 3), it remains relatively low compared to other major forms of cancers such as prostate (95%), breast (88%), and colorectal cancer (64%). The low survival rate may be explained in part due to patients' advanced clinical stage at the time of initial diagnosis, when the tumor has grown large and metastasized to other parts of the body.

Figure 3 Five-year survival rate for lung cancer in Canada in 1995-1999 and 2005-2009



Source: Lung Cancer Canada: 2015 Faces of Lung Cancer Report

2.3. Risk Factors, Signs, and Symptoms

Numerous factors have been identified as risk factors for developing lung cancer, including but not limited to tobacco consumption, age, sex, family history of lung cancer, and exposure to environmental factors such as radon, asbestos, and air pollution (Alberg et al., 2007; Anderson et al., 2003; Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2018; Gray et al., 2009; Lissowska et al., 2010; Straif et al., 2009).

Tobacco consumption has been identified as the leading cause of lung cancer development. The risk of developing lung cancer was estimated to be 20-40 times higher for lifelong smokers than non-smokers (Ozlü & Bülbül, 2005). It is estimated that the risk of developing lung cancer declines by 39% five years

after smoking cessation, although it will not return to that of never-smokers (Tindle et al., 2018). Exposure to second-hand smoke was identified as the next most common contributor to development of lung cancer. Non-smokers who have lived with smokers and were exposed to second-hand smoke had 20%-30% increased risk in developing lung cancer (U.S. Department of Health and Human Services, 2014). Exposure to radon-gas was the leading non-tobacco related cause of lung cancer; approximately 10% of all lung cancer incidence in Canada may be attributed to indoor radon exposure (Chen et al., 2012).

Lung cancer tends to be asymptomatic in its early stages. It has a long latency period where cancer cells grow for many years without being noticed; consequently, patients are often diagnosed in the advanced stages of disease, after the cancer has metastasized to other parts of the body. At its early stages, symptoms conform to other common diseases such as seasonal flu or common cold. Symptoms may include persistent cough, chest pains, weight loss, shortness of breath, fatigue, and hoarseness (American Cancer Society, 2016a, 2016b; National Cancer Institute, 2018). As cancer worsens and metastasize to the brain, liver, bone, and lymph nodes, symptoms such as severe coughs, swelling in the face or neck, difficulty in swallowing, pain in the bones, numbness in limbs, and jaundice become apparent enough to seek medical attention (American Cancer Society, 2016a, 2016b).

2.4. Screening & Testing

The Canadian Task Force on Preventive Health Care has recommended screening with low-dose computed tomography (LDCT) every year for three consecutive years for high-risk individuals (Canadian Task Force on Preventive Health Care, 2016). High-risk individuals are defined as adults between the age of 55 and 74 years with history of smoking within the past 15 years and at least a 30-pack year smoking history (Canadian Task Force on Preventive Health Care, 2016). The underlying principle of screening is to detect a disease in its early stages to enable the use of less invasive types of

treatments and decrease overall mortality. Since lung cancer is asymptomatic in its early stages, screening offers the possibility of identifying lung cancer patients that would otherwise go undetected. Detection of tumors at earlier stages can lead to improved prognosis and increased likelihood of treatment success. The five-year survival rate for stage IA NSCLC is 77-92% in Canada compared to 0-10% for stage IV NSCLC (Canadian Cancer Society's Advisory Committee on Cancer Statistics, 2017). Approximately 1.4 million Canadians have been classified as high-risk and were eligible for LDCT screening in 2018 (Evans et al., 2016).

Several tests are available and conducted to confirm the diagnosis of lung cancer. Tests may include x-rays, magnetic resonance imaging (MRI), positron emission tomography (PET) scans, and computed tomography (CT) scans to reveal an abnormal mass or nodule on the lungs (National Cancer Institute, 2018). CT scans are used to reveal small lesions in the lungs that may otherwise be undetected in x-rays, while MRIs are used to locate the tumor and/or metastases and measure the tumor's size. (American Cancer Society, 2016a, 2016b). Biopsy and pathology review may be performed to establish tissue diagnosis, which includes the use of immunohistochemistry (Canadian Cancer Society, 2021). In addition, blood tests such as complete blood count and platelets or metabolic profile are commonly conducted (Canadian Cancer Society, 2021). It is recommended that the first staging tests be the least invasive method with the highest diagnostic yield rate, which may include bronchoscopy with transbronchial needle aspiration, endobronchial ultrasound-guided needle aspiration, endoscopic ultrasound-guided needle aspiration, transthoracic needle aspiration, or mediastinoscopy (Canadian Cancer Society, 2021; Darling et al., 2018).Results from these tests are used to reveal specific characteristics of the lung cancer, which help determine prognosis and guide treatment selection.

2.5. Treatment

Treatment options can vary depending on one's overall health, along with the type and stage of the cancer. Treatment of lung cancer includes surgery (wedge resection, segmental resection, lobectomy, pneumonectomy), systemic therapy, radiation therapy, chemotherapy, radiosurgery, and supportive care (National Cancer Institute, 2018). There is no cure for patients with stage IIIB/IV NSCLC; therefore, palliative treatment is commonly used for advanced NSCLC to effectively manage symptoms. The below section outlines treatments by line of therapy for EGFR mutation-positive NSCLC.

2.5.1. First-line treatment – EGFR mutation-positive

For patients with sensitizing *EGFR* mutations, one of osimertinib (Tagrisso®, AstraZeneca), afatinib (Giotrif®, Boehringer Ingelheim), erlotinib (Tarceva®, Roche), or gefitinib (Iressa®, AstraZeneca) is recommended (Melosky et al., 2020). Gefitinib was the first EGFR-TKI to be approved by Health Canada in December 2003 as a third-line treatment for NSCLC. In December 2009, Health Canada approved expanded indication for gefitinib for use in the first-line setting for patients with *EGFR* activating mutations in tumor. Erlotinib was first approved in July 2005 and indicated as second- or third-line treatment for NSCLC (irrespective of the presence of *EGFR* mutations), following failure of first- or second- line chemotherapy. In August 2012, Health Canada approved an additional indication for erlotinib as a first-line therapy for patients with activating mutations in *EGFR* with NSCLC. Afatinib was approved by Health Canada in 2013 as a first-line monotherapy for the treatment of metastatic adenocarcinoma of the lung with activating *EGFR* mutations. Osimertinib was the first third-generation EGFR-TKI to receive Health Canada approval on July 2018 for treatment of locally advanced or metastatic NSCLC patients whose tumors have *EGFR* exon 19 deletions or exon 21 substitution mutations. The four TKIs are currently funded under the Exceptional Access Program in Ontario.

All four agents are orally administered and work to inhibit the activity of the EGFR tyrosine kinase, an enzyme that regulates the *EGFR* signaling pathway. All agents showed statistically significant improvements in PFS and overall response rate (ORR), along with minor improvements in OS compared to standard chemotherapy regimens in the first-line setting (Maemondo et al., 2010; Rosell et al., 2012; Yang et al., 2017; Zhou et al., 2011). Osimertinib is currently the preferred first-line treatment for patients with advanced NSCLC whose tumors harbor common *EGFR* mutations (exon19del and L858R); the phase III FLAURA trial demonstrated significant improvement in OS with osimertinib compared to first-generation EGFR-TKIs (Soria et al., 2018; Ramalingam et al., 2020). However, the upfront use of osimertinib in the first-line setting is associated with concerns about the restricted treatments options for later lines of therapy.

2.5.2. Second-line treatment – EGFR mutation-positive

For patients harboring *EGFR* mutations who did not respond to first-line EGFR TKIs, combination platinum-based cytotoxic chemotherapy is recommended (Ellis, 2016; Melosky et al., 2020). In addition, osimertinib is recommended for patients with acquired T790M mutation (Ellis, 2016; Melosky et al., 2020). For patients with an exon 20 insertion who progressed from first-line platinum-based cytotoxic chemotherapy, docetaxel is recommended (Melosky et al., 2020).

2.5.3. Third-line treatment – EGFR mutation-positive

For patients who progressed from platinum-based chemotherapy in the second-line setting, docetaxel is recommended (Melosky et al., 2020). For patients who acquired T790M mutation and received osimertinib in the second-line setting, platinum-based chemotherapy is recommended (Melosky et al., 2020).

2.6. Economic Burden of Lung Cancer

Lung cancer is associated with substantial economic burden for the health care system in Canada. In Ontario, the total direct cost for all NSCLC patients was $1.9 billion from 2010-2015, while the mean cost per patient was $76,816 (Seung et al., 2019). By 2040, direct costs associated with lung cancer could exceed $7.9 billion per year in Ontario (Smetanin et al., 2011).

Similar trends were observed in the US and Europe. In 2009, the total cost of cancer in the EU was €126 billion, of which lung cancer accounted for €18.8 billion or 15% of the overall cancer costs (Luengo-Fernandez et al., 2013). In 2015, the total cost of cancer in the US was $183 billion and the overall costs were projected to increase by 34% to $246 billion by 2030 (Mariotto et al., 2020). The economic burden of lung cancer is projected to rise globally in the coming years mainly due to the aging population and increases in the costs of associated treatments.

2.7. Cost-Effectiveness

Economic evaluation aims to quantify the comparative costs and benefits of adopting new intervention for health conditions versus continuing to use existing treatments for the same conditions (Drummond, 2015; Jakubiak-Lasocka & Jakubczyk, 2014). It provides a framework to systematically assess the combinational value of clinical evidence, health care costs, and other effects (e.g. quality of life) (Drummond, 2015). The main purpose of economic evaluations is to help policymakers optimize resource allocation decisions in health care.

One of the most widely used forms of economic evaluation is cost-effectiveness analysis (CEA). CEA allows us to examine the costs of alternative approaches to achieving a specific health outcome (Drummond, 2015; Leung, 2016). CEAs measure health benefits/outcomes in natural units (e.g. number of falls prevented), which are usually clinically relevant.

$$ICER = \frac{(C_T - C_C)}{(E_T - E_C)} = \frac{\Delta C}{\Delta E}$$

The main output of CEA is the incremental cost-effectiveness ratio (ICER), which is a summary measure representing the economic value of an intervention. The ratio statistic is calculated by dividing the difference in costs between the competing interventions (numerator) over the difference in effectiveness (denominator). The costs of the existing treatment are subtracted from the costs of the new intervention in the numerator, and the same is done with the measure of effectiveness in the denominator such that the ICER shows the cost of obtaining one additional unit of effect if one switches from the existing therapy to a new therapy (Cohen & Reynolds, 2008; Drummond, 2015; Hoch & Dewa, 2008). Once ICER is calculated, it is compared with a predefined threshold value, also known as willingness-to-pay threshold (WTP), to determine whether the intervention is cost-effective. Five possible outcomes can be inferred from the ICER. The intervention can be 1) more expensive and more effective, 2) more expensive and less effective (dominated), 3) less expensive and more effective (dominates), 4) less expensive and less effective, and 5) neutral (costs and effects are the same).

2.8. Cost-effectiveness of EGFR-TKIs

Numerous economic evaluations have been conducted to date, which assessed the cost-effectiveness of EGFR-TKIs across all settings. However, majority of the existing economic evaluations have either compared one EGFR-TKI to best supportive care (e.g., chemotherapy) or inferred efficacy/effectiveness estimates from indirect treatment comparisons using information derived from multiple trials. Of the existing literature, three studies compared an EGFR-TKI to best supportive care (Khan et al., 2015; Tan et al., 2018; Wen et al., 2018). Two studies compared afatinib and gefitinib (Chouaid et al., 2017; Wang et al., 2019), while one study compared erlotinib and gefitinib (Lee et al., 2014), and the remaining

studies compared multiple EGFR-TKIs simultaneously (Arrieta et al., 2020; Gu et al., 2019; Holleman et al., 2020; Kimura et al., 2018; Ting et al., 2015; Yang et al., 2020).

Apart from studies which investigated the cost-effectiveness of EGFR-TKIs using observational data (Arrieta et al., 2020; Yang et al., 2020) or the LUX-Lung 7 trial (Chouaid et al., 2017; Wang et al., 2019) where head-to-head data were available, other studies have sourced information from multiple trials and indirectly compared the efficacy/effectiveness estimates to calculate the ICER. Studies have reported differing results with varying ranges of ICERs and no clear patterns. Therefore, there is no concrete evidence to suggest which EGFR-TKI is the most cost-effective option. A summary of the study findings is reported in Table 3.

Table 3. Summary of cost-effectiveness studies of EGFR-TKIs for NSCLC

Author	Year	Country	Perspective	Therapy	Data Sources	ICER
Arrieta et al.	2020	Mexico	Payer	Afatinib, Erlotinib, Gefitinib	Medical records at Instituto Nacional de Cancerologia (INCan)	Erlotinib dominated by afatinib and gefitinib PFS: Afatinib vs. Gefitinib: $145,625 MXN/LY OS: Afatinib vs. Gefitinib: $18,640 MXN/LY
Chouaid et al.	2017	France	Payer	Afatinib vs. Gefitinib	Lux-Lung 7	ITT: €45,211/QALY Exon Leu858Arg: €52,518/QALY Exon 19 Del: €38,970/QALY
Gu et al.	2019	China	Payer	Afatinib vs. Erlotinib, Gefitinib, PC	Lux-Lung 3, Lux-Lung 6, Lux-Lung 7, First-SIGNAL, OPTIMAL, EURTAC, ENSURE, IPASS, NEJ002, WJTOG3405	Afatinib vs. PC: $20,758/QALY Afatinib vs. Gefitinib: $17,693/QALY Afatinib vs. Erlotinib: $16,197/QALY
Holleman et al.	2020	The Netherlands	Payer	Afatinib, Erlotinib, Gefitinib, Osimertinib	NEJ002, WJTOG3405, IPASS, First-SIGNAL, OPTIMAL, EURTAC, ENSURE, Lux-Lung 3, Lux-Lung 6, Lux-Lung 7, CTRONG0901, FLAURA	Gefitinib dominated by Erlotinib Afatinib vs. Erlotinib: €27,058/LY and €41,504/QALY Osimertinib vs. Afatinib: €91,726/LY and €128,343/QALY
Khan et al.	2015	UK	Payer	Erlotinib vs. BSC	TOPICAL	Erlotinib vs. BSC: £202,571/QALY
Kimura et al.	2018	Japan	Payer	Gefitinib vs. Afatinib, Erlotinib	RCTs - not specified	Gefitinib vs. Afatinib: 122,070/MST (JPY) Gefitinib vs. Erlotinib: 69,605/MST (JPY)
Lee et al.	2014	China	Not Specified	Erlotinib vs. Gefitinib	OPTIMAL, IPASS, NEJGSG, WJTOG	Erlotinib vs. Gefitinib: $62,419/QALY
Tan et al.	2018	Singapore	Payer	Afatinib vs. PC	Lux-Lung 3	Afatinib vs. PC: SG$137,648/QALY and SG$109,172/LY
Ting et al.	2015	US	Societal	Erlotinib vs. Afatinib, PC	EURTAC, Lux-Lung 3	Erlotinib vs. Afatinib: $61,809/QALY Erlotinib vs. PC: $40,106/QALY
Wang et al.	2018	China	Payer	Afatinib vs. Gefitinib	Lux-Lung 7	ITT: $9820/QALY Exon Leu858Arg: $18,530/QALY Exon 19 Del: $1586/QALY
Wen et al.	2018	China	Payer	GC vs. Erlotinib	OPTIMAL, ENSURE	GC vs. Erlotinib: $174,808/QALY
Yang et al.	2020	Taiwan	Payer	Afatinib, Erlotinib, Gefitinib	Records from National Cheng Kung University Hospital	Afatinib dominated by Erlotinib Erlotinib vs. Gefitinib: $17,960/LY and $12,782/QALY

Chapter 3: Real-World Effectiveness of Nivolumab in Patients with Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis

3.1. Abstract

Background: The effectiveness of PD-1 checkpoint inhibitors for non-small-cell lung cancer under real-world clinical settings remains uncertain. **Materials & methods**: Systematic searches of PubMed, EMBASE and Web of Science were conducted. Random-effects models were used to estimate pooled median overall survival and progression-free survival estimates. **Results**: 36 studies of nivolumab were included for narrative synthesis and 11 of these studies were included for meta-analysis. Age, sex, histology and prior lines of treatment did not affect survival outcomes, while Eastern Cooperative Oncology Group Performance Status and brain metastasis were inversely associated with survival. In the meta-analysis, nivolumab was associated with 9.6 months (95% CI: 8.4–10.9) of overall survival and 2.6 months (95% CI: 1.6–3.6) of progression-free survival. **Conclusion**: Very-low-certainty evidence suggested the real-world effectiveness of nivolumab was consistent with those observed in the clinical trials.

3.2. Introduction

The epidemiology of lung cancer is specified in Chapter 2 of this thesis. While many first-line treatments for NSCLC are available, the number of second-line therapies remains limited. Recent development of immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 pathway have shown increased survival over standard of care docetaxel-based chemotherapy in the second-line treatment of persons with advanced/metastatic NSCLC (Borghaei et al., 2015; Brahmer et al., 2015; Reck et al., 2016).

Nivolumab (Opdivo; Bristol-Myers Squibb, NJ, USA) was the first ICI to be approved by the US Food and Drug Administration (FDA) for treating patients with advanced NSCLC following first-line platinum-based chemotherapy. In the CheckMate-017 trial, nivolumab was associated with improved OS, PFS and ORR compared to docetaxel in patients with pre-treated squamous lung carcinoma (Brahmer et al., 2015). Similarly, in the CheckMate-057 trial, conducted in recurrent nonsquamous patients, nivolumab was shown to improve OS and ORR over docetaxel, but not PFS (Borghaei et al., 2015). In the CheckMate-026 trial, administration of nivolumab as first-line treatment in patients with PD-L1-positive NSCLC was associated with similar OS and PFS, and lower ORR compared with platinum-based chemotherapy (Carbone et al., 2017).

Although randomized controlled trials (RCTs) are the gold-standard approach to assessing the safety and efficacy of therapeutic interventions, trial results often do not reflect the effectiveness of therapy in clinical practice. The gap between efficacy and effectiveness may be bridged by real-world studies in clinical practice, which often complement RCTs by investigating a wider spectrum of patients with more diverse demographic profiles, prognoses and comorbidities. We undertook this systematic review and meta-analysis to evaluate the effectiveness of nivolumab therapy in real-world settings and to compare the results in these settings with the findings of RCTs.

3.3. Materials and Methods

3.3.1. Search Strategy

The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 5 April 2019 (CRD 42019127837). This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses (PRISMA) guideline (Moher et al., 2009). We searched PubMed, EMBASE and Web of Science to identify studies published between March 2015 and March 2019. The March 2015 start date coincided with the FDA's approval of the first immunotherapy (nivolumab) for treating NSCLC. A medical librarian helped develop the search strategy and tailor it for each database. Reference lists of all eligible studies were searched to find additional publications. Only English-language studies published in peer-reviewed journals were considered for inclusion (Appendix A)

3.3.2. Study Selection

We included any type of observational study reporting OS or PFS in clinical practice. Interventions included atezolizumab, nivolumab or pembrolizumab for treating NSCLC, regardless of whether the treatment was used as first- or second-line therapy, or in some other therapeutic manner. We excluded case reports, RCTs, conference abstracts, letters to the editor, narrative reviews and systematic reviews/meta-analyses.

Article titles and abstracts were screened independently by two reviewers (YJ Kim and D Shah) to identify citations that might satisfy the eligibility criteria. These citations advanced to full-text screening, where they were again independently evaluated by the two reviewers (YJ Kim and D Shah). The reviewers resolved discrepancies through consensus or referred articles to a third reviewer (S Horton) for arbitration in the absence of consensus. Additional citations identified through the reference lists of included articles were screened as previously described.

3.3.3. Data Extraction

Data extraction was conducted independently by two reviewers (YJ Kim and D Shah) using a standardized data extraction form. Disagreements between reviewers were resolved by consensus

or by a third reviewer (S Horton). We extracted the following data from the studies: author, year of publication, country, intervention, design, study population, sample size, age, sex, smoking status, line of therapy, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), stage, histological subtype, metastasized sites, biomarker summary, follow-up period, treatment cycles, median OS and median PFS with 95% CI, and proportion of adverse events.

3.3.4. Quality Assessment

Risk of bias was assessed using the Newcastle–Ottawa Scale (NOS) – Cohort Studies (Wells et al., 2019). To assess included case-series, we modified the NOS and excluded the sections related to 'selection of the nonexposed cohort' and 'comparability of the cohort'; the scores on the modified NOS ranged from zero stars (high risk of bias) to six stars (low risk of bias). Risk of bias assessment was performed independently by the two reviewers (YJ Kim and D Shah). Discrepancies were resolved by consensus or referred to a third reviewer (S Horton) for arbitration in the absence of consensus. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (Dijkers, 2013) was used to assess the certainty of evidence for OS and PFS.

3.3.5. Data Synthesis and Analysis

A narrative synthesis was conducted on all included studies, with the synthesis being stratified by variables including age, sex, histology, prior lines of treatment, brain metastasis, and ECOG-PS. Separate random effects meta-analyses following McGrath et al.'s procedure (McGrath et al., 2020; McGrath et al., 2019) were conducted for median OS and PFS. Studies were meta-analyzed if they satisfied the following criteria: reported on the administration of nivolumab at 3 mg/kg per 2 weeks, contained similar median follow-up times, and reported a sufficient degree

of quantitative data to permit inclusion in meta-analysis (e.g., presented Kaplan–Meier curves to permit us obtain study-specific minimum and maximum values to estimate pooled median OS and PFS). Furthermore, in the meta-analysis, we included studies with samples drawn from broad-based populations, and we excluded studies using samples chosen from narrowly defined population.

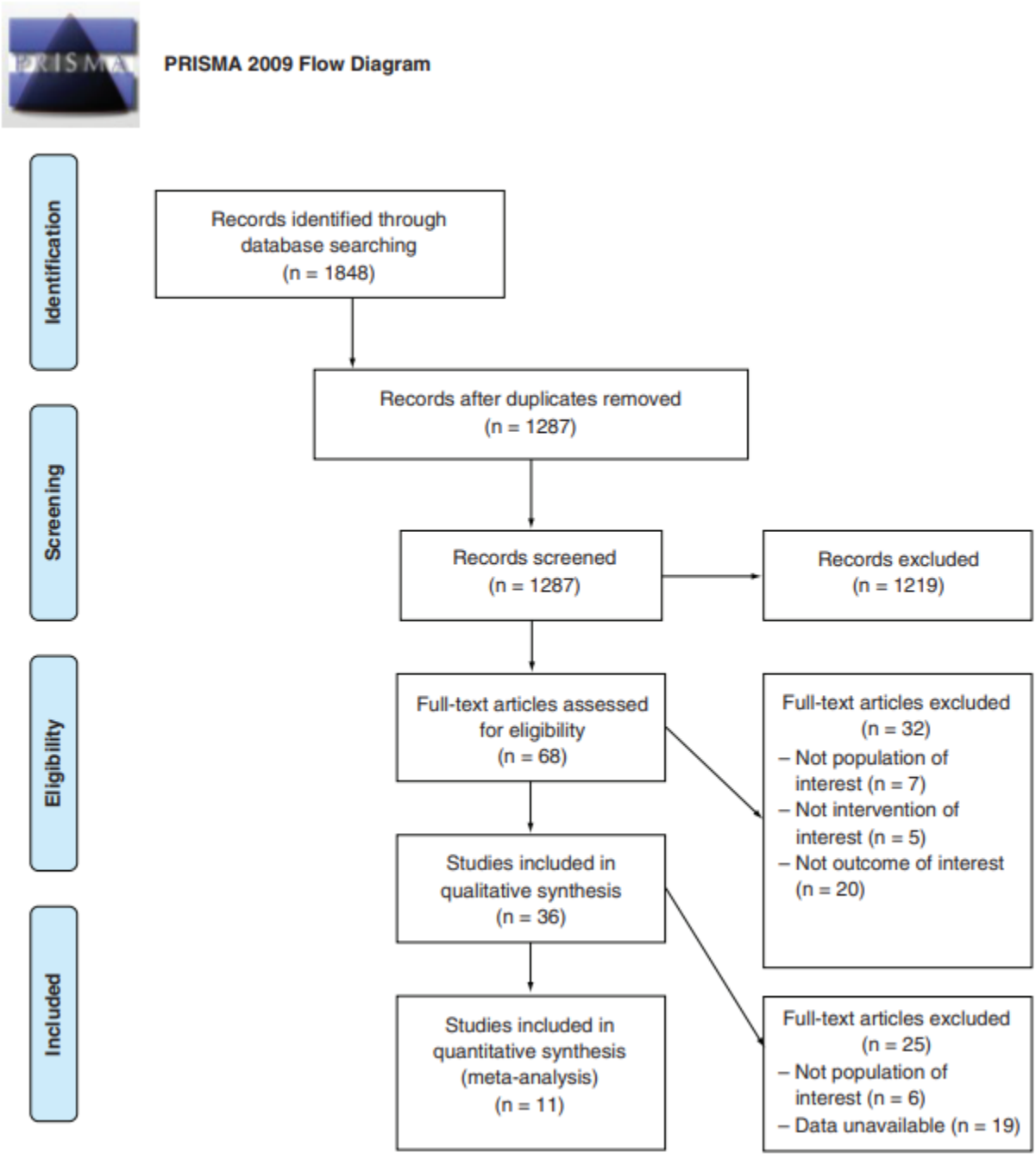
Statistical heterogeneity was assessed using the I^2 statistic and tested with Cochran's Q statistic and its associated p-value. Substantial heterogeneity was considered to be present when I^2 >50% and $p < 0.10$. We decided a priori to assess publication bias with funnel plots if ten or more articles were included in a meta-analysis. The meta-analyses were conducted using the 'meta-median' package in R v3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria).

3.4. Results

3.4.1. Search Results

The flow chart detailing study selection is depicted in Figure 4. The literature search identified 1848 citations from the three databases. After removing duplicates and screening titles, abstracts, and full texts, we identified 36 studies for inclusion in the review and 11 studies for meta-analysis. Our literature search did not yield any articles on atezolizumab and identified only one study on pembrolizumab (Ksienski et al., 2019); therefore, all included articles focused only on nivolumab.

Figure 4. Flow diagram of study selection



3.4.2. Study Characteristics and Quality Assessment

The characteristics of the included studies are shown in Table 4. The studies were retrospective (n = 31), prospective (n = 4) or unknown (n = 1). The studies were either case-series (n = 33) or

cohort (n = 3). All case-series studies assessed outcomes associated with nivolumab. One cohort study compared effectiveness between nivolumab and docetaxel (Calpe-Armero et al., 2017), while another compared effectiveness between nivolumab and pembrolizumab (Ksienski et al., 2019). The third cohort study compared effectiveness of nivolumab at a standard-dose of 3 mg/kg per 2 weeks to a low-dose of 20/100 mg per 3 weeks (Yoo et al., 2018). The studies were carried out in multicenter (n = 21) or single center (n = 15) settings.

The studies contained a total of 6504 participants, with sample sizes ranging from 19 to 1588 (mean = 181). The mean or median ages ranged from 58 to 71 years. The percentage of males enrolled in the 36 studies ranged from 39 to 100% (mean = 66.6%). The included studies generally had low risk of bias, with most scoring 4 to 6 on the NOS among case-series and 6 to 7 among cohort studies (Appendix B).

Table 4 Characteristics of the included studies

Author	Year/ Country	Intervention (Drug, Dose/Week)	Histologic Subtype (%)	Sample Size	Prior Lines of Treatment (%)	Site of Metastasis (%)	Median OS (95% CI), Months	Median PFS (95% CI), Months
Areses Manrique et al.	2018/ Spain	Nivolumab 3mg/kg per 2 weeks	Adenocarcinoma - 60 Squamous - 35 NOS - 5	188	1 – 117 (62) 2 – 45 (24) ≥3 – 26 (14)	CNS – 42 (22)	12.85 months (95%CI: 9.07 - 16.62)	4.83 months (95%CI: 3.69 - 5.97)
Bagley et al.	2017/ US	Nivolumab 3mg/kg per 2 weeks	Squamous - 24 Non-squamous - 76	175	1 – 94 (54) 2 – 44 (25) ≥3 – 37 (21)	Bone – 86 (49) Brain – 55 (31) Liver – 41 (23)	6.5 months (95%CI: 5.2-8.0)	2.1 months (95%CI: 1.9-2.6)
Brustugun, Sprauten & Helland	2017/ Norway	Nivolumab 3 mg/kg per 2 weeks	Adenocarcinoma - 55.2 Squamous - 41.4 Large cell - 1.7 Adenosquamous - 1.7	58	1 – 20 (34.5) 2 – 27 (46.6) ≥3 – 11 (18.9)	NR	11.7 months (95%CI: NR)	NR
Calpe-Armero et al.	2017/ Spain	Nivolumab 3mg/kg per 2 weeks vs. Docetaxel 75 mg/m^2 per 3 weeks	Nivolumab - Squamous - 21 Non-squamous - 79 Docetaxel - Squamous - 21 Non-squamous - 79	Overall-3 Nivolumab-14 Docetaxe-19	NR	NR	Nivolumab - Not achieved Docetaxel - 4.24 months (95%CI: 3.49-9.87)	Nivolumab - 2.76 months (95%CI: 1.28-9.87) Docetaxel - 2.0 months (95%CI: 1.58-2.50)
Costantini et al.	2018/ France	Nivolumab 3mg/kg per 2 weeks	Squamous - 28 Adenocarcinoma - 61 Giant - 7	303	1 – 120 (40) 2 – 88 (29) ≥3 – 94 (31)	Lung – 120 (40) Pleura – 88 (29) CNS – 62 (20) Liver – 48 (16) Adrenal Gland – 54 (18) Bone – 78 (26)	11.3 months (95%CI: 8.5-13.8)	2.6 months (95%CI: 2.1-3.5)
Crino et al.	2019/ Italy	Nivolumab 3mg/kg per 2 weeks	Non-squamous - 100	1588	1 – 378 (24) 2 – 562 (36) ≥3 – 639 – (40) Unknown – 9 (1)	CNS – 409 (26) Bone – 327 (21) Liver – 626 (39)	11.3 months (95%CI: 10.2 - 12.4)	3.0 months (95%CI: 2.9 - 3.1)

Author	Year/ Country	Intervention (Drug, Dose/Week)	Histologic Subtype (%)	Sample Size	Prior Lines of Treatment (%)	Site of Metastasis (%)	Median OS (95% CI), Months	Median PFS (95% CI), Months
Diem et al.	2017/ Switzerland	Nivolumab 3mg/kg per 2 weeks	Squamous - 35 Adenocarcinoma - 58	52	0 – 2 (4) 1 – 29 (56) 2 – 13 (25) ≥3 – 8 (16)	Bone – 17 (33) Liver – 17 (33) Lung – 15 (29) Brain – 15 (29) Adrenal – 10 (19) Pleura – 9 (17) Soft tissue – 6 (12)	9.6 months (95%CI: 6-14)	2.1 months (95%CI: 1.8-6.4)
Dudnik et al.	2018/ Israel	Nivolumab 3mg/kg per 2 weeks	Squamous - 23 Non-squamous - 70 Other - 6 NR - 1	260	0 – 15 (6) 1 – 167 (64) ≥2 – 68 (26) NR – 10 (4)	Brain – 55 (21) Liver – 55 (21)	5.9 months (95%CI: 4.7-7.4)	2.8 months (95%CI: 1.8 - 7.7)
Dumenil et al.	2018/ France	Nivolumab 3mg/kg per 2 weeks	Squamous - 25 Adenocarcinoma - 70 Others - 5	67	NR	CNS – 11 (16)	6.3 months (IQR - 3.1 - 13.5)	3 months (IQR - 1.6 - 6.6)
Facchinetti et al.	2018/ Italy	Nivolumab 3mg/kg per 2 weeks	Squamous - 48 Non-squamous - 52	54	NR	Lymph Node – 48 (88) Liver – 8 (15) Bone – 16 (30) Adrenal Gland – 8 (17) Brain – 7 (13) Contralateral Lung – 27 (50) Pleura – 19 (38) Other – 14 (26)	5.7 months (95%CI: 0.4-17.7)	2.5 months (95%CI: 1.5-3.5)
Fiorica et al.	2018/ Italy	Nivolumab 3mg/kg per 2 weeks	Squamous - 54 Non-squamous - 46	35	1 – 27 (77) 2 – 5 (14) 3 – 3 (9)	Lung – 16 (46) Bone – 8 (23) Lymph Node – 12 (34) Liver – 5 (14)	8.7 months (95%CI: 4.1-13.2)	NR
Fujimoto et al.	2019/ Japan	Nivolumab 3mg/kg per 2 weeks	Squamous - 24 Non-squamous - 66 NOS - 6 Other - 4	542	1 – 180 (33) 2 – 136 (25) ≥3 – 226 (42)	NR	16.1 months	2.6 months
Fukui et al.	2019/ Japan	Nivolumab 3mg/kg per 2 weeks	Squamous - 31 Adenocarcinoma - 63 NOS - 6	52	1 – 22 (42) 2 – 15 (29) ≥3 – 15 (29)	Brain – 8 (15) Lung – 22 (42) Liver – 10 (19) Bone – 16 (31)	NR	2.1 months (95%CI: 1.0-3.2)

Author	Year/ Country	Intervention (Drug, Dose/Week)	Histologic Subtype (%)	Sample Size	Prior Lines of Treatment (%)	Site of Metastasis (%)	Median OS (95% CI), Months	Median PFS (95% CI), Months
Garde-Noguera et al.	2018/ Spain	Nivolumab 3mg/kg per 2 weeks	Squamous - 23 Non-squamous - 77	175	1 – 65 (37) 2 – 66 (38) ≥3 – 44 (25)	Brain – 38 (22) Lung – 115 (67) Liver – 39 (23) Bone – 67 (39) Adrenal Gland – 31 (18) Lymph Node – 100 (58) Soft Tissue – 19 (11)	5.81 months (95%CI: 3.74-7.88)	2.69 months (95%CI: 2.01-3.37)
Garassino et al.	2018/ Italy	Nivolumab 3mg/kg per 2 weeks	Squamous - 100	371	1 – 162 (44) 2 – 120 (32) ≥3 – 89 (24)	CNS – 37 (10) Liver – 63 (17) Bone – 120 (32)	7.9 months (95%CI: 6.2 - 9.6)	4.2 months (95%CI: 3.4 - 5.0)
Grossi et al.	2018/ Italy	Nivolumab 3mg/kg per 2 weeks	Squamous - 100	371	1 – 162 (44) 2 – 120 (32) ≥3 – 89 (24)	Brain – 37 (10) Liver – 63 (17) Bone – 120 (32	7.9 months (95%CI: 6.2 - 9.6)	4.2 months (95%CI: 3.4 - 5.0)
Haratani et al.	2017/ Japan	Nivolumab 3mg/kg per 2 weeks	Pre-TKI: Adenocarcinoma - 96 Squamous - 4 Post-TKI: Adenocarcinoma - 72 NOS - 12 Not examined - 16	25	1 – 28 (33) 2 – 21 (25) ≥3 – 36 (42)	CNS – 14 (16)	Not reached	1.5 months (95%CI: 1.3-2.8)
Juergens et al.	2018/ Canada	Nivolumab 3 mg/kg per 2 weeks	Squamous - 26.3 Non-squamous - 73.1 Others - 0.6	472	1 – 209 (44) 2 – 138 (29) ≥3 – 125 (27)	CNS – 62 (13)	12.0 months (95%CI: 11.0 - 13.9)	NR
Kataoka et al.	2018/ Japan	Nivolumab 3mg/kg per 2 weeks	Squamous - 24 Non-squamous - 76	189	1 – 14 (7) 2 – 32 (17) ≥3 - 143 (76)	NR	NR	2.4 months
Kiriu et al.	2018/ Japan	Nivolumab 3mg/kg per 2 weeks	Squamous - 32 Adenocarcinoma - 53 Other - 15	19	1 – 5 (26) 2 – 9 (47) ≥3 – 5 (26)	NR	10.8 months	iNLR (increase in NLR) - 1.8 months sNLR (stable or decreased NLR)- 9.3 months
Kobayashi et al.	2018/ Japan	Nivolumab 3mg/kg per 2 weeks	Adenocarcinoma - 58.5 Squamous - 28.9 NOS - 6.3	142	1 – 57 (40) ≥2 – 85 (60)	CNS – 27 (19)	NR	1.9 months (1.6 - 2.2)

Author	Year/ Country	Intervention (Drug, Dose/Week)	Histologic Subtype (%)	Sample Size	Prior Lines of Treatment (%)	Site of Metastasis (%)	Median OS (95% CI), Months	Median PFS (95% CI), Months
Ksienski et al.	2019/ Canada	Nivolumab 3mg/kg per 2 weeks Pembrolizumab 2mg/kg per 3 weeks	Nivolumab: Squamous - 25.7 Non-squamous - 74.3 Pembrolizumab: Squamous - 19.5 Non-squamous - 80.5	271 Nivolumab: 230 Pembrolizumab: 41	Nivolumab: 0 – 4 (2) 1 – 165 (72) ≥2 – 61 (26) Pembrolizumab: 0 – 17 (42) 1 – 19 (46) ≥2 – 5 (12)	Nivolumab: Brain – 30 (13) Liver – 28 (12) Pembrolizumab: Brain – 6 (15) Liver – 5 (12)	Nivolumab: 9.2 months (95%CI: 7.8-12.4) Pembrolizumab: 13.5 months (95%CI: 10.62-NR)	Nivolumab: 5.7 months (95%CI: 4.1-8.8) Pembrolizumab: 13.5 months (95%CI: 8.2-NR)
Lesueur et al.	2018/ France	Nivolumab	Adenocarcinoma - 32.7 Squamous - 62.5 Other - 4.8	104	0-1 – 57 (55) 2 - 31 (30) ≥3 – 16 (15)	Brain – 46 (44)	11.1 months (95%CI: 5.8 - 16.5)	2.7 months (95%CI: 1.4 - 4.1)
Merino Almazan et al.	2019/ Spain	Nivolumab 3mg/kg per 2 weeks	Squamous - 59.7 Non-squamous - 38	221	NR	Lung – 115 (52) Lymph Node – 72 (33) Bone – 69 (31) Liver – 41 (19) Brain – 22 (10)	9.7 months (95% CI: 7.6 - 11.8)	5.3 months (95% CI: 3.2-7.3)
Montana et al.	2019/ France	Nivolumab 3 mg/kg per 2 weeks	Squamous - 21.4 Non-squamous - 78.6	98	0-1 – 44 (45) ≥2 – 54 (55)	NR	6.34 months (95% CI: 4.11 - 10.88)	1.84 months (95% CI: 1.68 - 2.73)
Sabatier et al.	2018/ France	Nivolumab 3mg/kg per 2 weeks	Squamous - 37 Non-squamous - 63	30	1 – 20 (67) 2 – 4 (13) ≥3 – 6 (20)	NR	7.1 months (95%CI: 4.9 - 9.4)	3.3 months (95%CI: 2.7 - 3.9)
Sato et al.	2018/ Japan	Nivolumab 3mg/kg per 2 weeks	Squamous - 26 Non-squamous - 74	38	NR	NR	NR	2.9 months (95%CI: 1.55 - NR)
Schmid et al.	2018/ Switzerland	Nivolumab 3mg/kg per 2 weeks	Squamous - 35 Adenocarcinoma - 58	52	0 – 2 (4) 1 – 29 (56) 2 – 13 (25) ≥3 – 8 (16)	NR	11.9 months	2.3 months

Author	Year/ Country	Intervention (Drug, Dose/Week)	Histologic Subtype (%)	Sample Size	Prior Lines of Treatment (%)	Site of Metastasis (%)	Median OS (95% CI), Months	Median PFS (95% CI), Months
Schouten et al.	2018/ The Netherlands	Nivolumab 3 mg/kg per 2 weeks	Adenocarcinoma - 66.5 Squamous cell - 22.2 Mixed - 6.5 Unspecified - 4.8	248	0–2 (0.8%) 1–185 (74.6%) 2 - 44 (17.7%) 3 – 14 (5.7%) >3 – 3 (1.2%)	Brain – 56 (23)	10.0 months (95% CI: 6.65-13.35)	2.6 months (95% CI: 2.38 - 2.82)
Sekine et al.	2018/ Japan	Nivolumab 3mg/kg per 2 weeks	Squamous - 11.5 Adenocarcinoma - 73.6 Other - 14.9	87	0 – 2 (2) 1 – 23 (27) 2 – 34 (39) ≥3 – 28 (32)	NR	12.5 months (95%CI: 8.8-13.7)	3.0 months (95%CI: 2.6-4.4)
Shamai & Merimsky	2018/ Israel	Nivolumab 3 mg/kg per 2 weeks	Squamous - 16.89 Non-squamous - 83.11	77	0 – 3 (4) 1 – 43 (56) 2 – 14 (18) ≥3 – 17 (22)	NR	8 months (NR)	4 months (NR)
Shiroyama et al.	2018/ Japan	Nivolumab 3mg/kg per 2 weeks	Squamous - 20.4 Non-squamous - 79.6	201	Median – 2	NR	NR	2.9 months (95%CI: 2.1-3.7)
Takeda et al.	2018/ Japan	Nivolumab 3mg/kg per 2 weeks	Squamous - 30 Adenocarcinoma - 70	30	1 – 8 (27) 2 – 9 (30) ≥3 – 13 (43)	NR	NR	2.6 months (95%CI: 1.3-4.9)
Tiu et al.	2018/ US	Nivolumab 3mg/kg per 2 weeks	Squamous - 13 Adenocarcinoma - 71 Mixed - 5 Other - 11	38	NR	Contralateral lobe – 9 (24) Pleural nodules – 6 (16) Pleural/Pericardial Effusion – 8 (21) Extrathoracic Organs – 25 (66)	21.4 months (95%CI: 13.5 - 27.4)	6.3 months (95%CI: 2.3 - 8.0)

Author	Year/ Country	Intervention (Drug, Dose/Week)	Histologic Subtype (%)	Sample Size	Prior Lines of Treatment (%)	Site of Metastasis (%)	Median OS (95% CI), Months	Median PFS (95% CI), Months
Tournoy et al.	2018/ Belgium	Nivolumab	Squamous - 26.6 Non-squamous - 73.4	267	1 – 138 (51.7) 2 – 87 (32.6) 3 – 32 (12.0) 4 – 8 (3.0) 5 – 2 (0.7)	Pulmonary – 140 (52) Bone – 115 (43) Extrathoracic lymph nodes – 64 (24) Liver – 55 (21) Brain – 46 (17) Adrenal Gland – 46 (17)	7.8 months (95%CI: 6.3-9.3)	3.7 months (95%CI: 2.9-4.5)
Yoo et al.	2018/ Korea	Nivolumab Standard: 3mg/kg per 2 weeks Low dose: 100 or 20mg every 3 week	Adenocarcinoma - 61.7 Squamous - 14.9 Other - 23.4	47	Overall: 1 – 18 (38) 2 – 16 (34) ≥3 – 13 (28) Standard: 1 – 13 (45) 2 – 10 (34) 3 – 6 (21) Low-dose: 1 – 5 (28) 2 – 6 (29) 3 – 7 (33)	NR	Overall: 12.5 months (95%CI: 6.5 - NR) Standard: 8.2 months (95%CI: 3.1-NR) Low-dose: 12.5 months (95%CI: 7.0-NR)	Overall: 1.1 months (95%CI: 0.8-3.0) Standard-dose: 1.0 months (95%CI: 0.6-1.7) Low-dose: 3.0 months (95% CI: 0.8-NR)

CI – Confidence Interval; OS - Overall Survival; PFS – Progression-Free Survival; NR – Not Reported

3.4.3. Overall Survival

Thirty studies reported OS outcomes (Areses Manrique et al., 2018; Bagley et al., 2017; Brustugun et al., 2017; Calpe-Armero et al., 2017; Costantini et al., 2018; Crinò et al., 2019; Diem et al., 2017; Dudnik et al., 2018; Dumenil et al., 2018; Facchinetti et al., 2018; Fiorica et al., 2018; Fleischman et al., 2016; Fujimoto et al., 2019; Garassino et al., 2018; Garde-Noguera et al., 2018; Grossi et al., 2018; Haratani et al., 2017; Juergens et al., 2018; Kiriu et al., 2018; Kobayashi et al., 2018; Ksienski et al., 2019; Lesueur et al., 2018; Merino Almazán et al., 2019; Montana et al., 2019; Sabatier et al., 2018; Schmid et al., 2018; Schouten et al., 2018; Sekine et al., 2018; Shamai & Merimsky, 2018; Tiu et al., 2018; Tournoy et al., 2018; Yoo et al., 2018). The median follow-up period was 1 year or less in ten studies (Crinò et al., 2019; Fiorica et al., 2018; Garassino et al., 2018; Grossi et al., 2018; Juergens et al., 2018; Ksienski et al., 2019; Sabatier et al., 2018; Schouten et al., 2018; Takeda et al., 2018; Yoo et al., 2018) and >1 year in six studies (Bagley et al., 2017; Calpe-Armero et al., 2017; Diem et al., 2017; Dumenil et al., 2018; Ksienski et al., 2019; Sato et al., 2018). In studies with median follow-up periods of <1 year, the median OS associated with nivolumab ranged from 7.1 (Sabatier et al., 2018) to 21.4 months (Tiu et al., 2018). In studies with median follow-up periods of ≥1 year, the median OS ranged from 4.0 (Facchinetti et al., 2018) to 11.9 months (Schmid et al., 2018). Median OS reported by Tiu et al. (21.4 months) was substantially longer than what authors reported in the other studies (Tiu et al., 2018). In two studies, half of the participants did not experience the outcome by the end of the study and thus, median OS associated with nivolumab was not reached (NR) (Calpe-Armero et al., 2017; Yoo et al., 2018).

Twenty-seven studies were case-series and three were cohort studies (Calpe-Armero et al., 2017; Ksienski et al., 2019; Yoo et al., 2018). In case-series studies of nivolumab, median OS ranged from 5.7 (Facchinetti et al., 2018) to 21.4 months (Tiu et al., 2018). In cohort studies, Ksienski et al.

reported median OS of 9.2 (95% CI: 7.8–12.4) and 13.5 months (95% CI: 10.62–NR) for nivolumab and pembrolizumab, respectively, while it was NR in a study by Calpe-Armero et al. (Calpe-Armero et al., 2017; Ksienski et al., 2019). Yoo et al. reported median OS of 8.2 (95% CI: 3.1–NR) and 12.5 months (95% CI: 7.0–NR) for standard and low-dose nivolumab therapy, respectively (Yoo et al., 2018).

Summary of median OS stratified by age, sex, ECOG-PS, histology, line of therapy and brain metastasis can be found in the Appendix C. For the most part, age, sex, histology and line of therapy did not appear to affect median OS. Exceptions were one study where male sex was negatively associated with OS (hazard ratio [HR]: 1.67; 95% CI: 1.05–2.64) (Grossi et al., 2018). Two other studies identified a statistically significant improvement in OS for persons with squamous histology compared with nonsquamous histology, with adjusted HR (aHRs) of 0.47 (95% CI: 0.25–0.91) (Schouten et al., 2018) and 0.59 (95% CI: 0.38–0.91) (Merino Almazán et al., 2019), respectively.

Statistically significant differences in survival were observed according to ECOG-PS. Eight studies reported median OS stratified by ECOG-PS (Areses Manrique et al., 2018; Dudnik et al., 2018; Facchinetti et al., 2018; Juergens et al., 2018; Merino Almazán et al., 2019; Montana et al., 2019; Schouten et al., 2018; Tournoy et al., 2018) with greater survival generally found in persons with lower ECOG-PS. The highest median OS was seen among patients with an ECOG-PS of 0 because the median OS was NR in two studies (Areses Manrique et al., 2018; Tournoy et al., 2018). The lowest OS was reported among patients with ECOG-PS of ≥2, with a median OS of 1.8 months (Facchinetti et al., 2018). Brain metastasis was another factor significantly associated with OS. Six studies reported median OS stratified by brain metastasis (Areses Manrique et al., 2018; Crinò et al., 2019; Dudnik et al., 2018; Facchinetti et al., 2018; Juergens et al., 2018; Schouten et al., 2018).

Compared with patients having no brain metastases, shorter median OS was reported for those with brain metastases (Areses Manrique et al., 2018; Crinò et al., 2019; Dudnik et al., 2018; Juergens et al., 2018; Schouten et al., 2018).

3.4.4. Progression-free Survival

Thirty-three studies reported median PFS (Areses Manrique et al., 2018; Bagley et al., 2017; Calpe-Armero et al., 2017; Costantini et al., 2018; Crinò et al., 2019; Diem et al., 2017; Dudnik et al., 2018; Dumenil et al., 2018; Facchinetti et al., 2018; Fujimoto et al., 2019; Fukui et al., 2019; Garassino et al., 2018; Garde-Noguera et al., 2018; Grossi et al., 2018; Haratani et al., 2017; Kataoka et al., 2018; Kiriu et al., 2018; Kobayashi et al., 2018; Ksienski et al., 2019; Lesueur et al., 2018; Merino Almazán et al., 2019; Montana et al., 2019; Sabatier et al., 2018; Sato et al., 2018; Schmid et al., 2018; Schouten et al., 2018; Sekine et al., 2018; Shamai & Merimsky, 2018; Shiroyama et al., 2018; Takeda et al., 2018; Tiu et al., 2018; Tournoy et al., 2018; Yoo et al., 2018). It is worth noting that as all included studies were observational in nature, PFS was assessed through sets of pre-defined proxy measures (e.g., initiation of 2L treatment) rather than assessment as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria as set forth in clinical trials. Nineteen of the thirty-three studies (Calpe-Armero et al., 2017; Costantini et al., 2018; Crinò et al., 2019; Dudnik et al., 2018; Facchinetti et al., 2018; Fukui et al., 2019; Garassino et al., 2018; Grossi et al., 2018; Haratani et al., 2017; Kataoka et al., 2018; Ksienski et al., 2019; Lesueur et al., 2018; Sabatier et al., 2018; Sato et al., 2018; Schmid et al., 2018; Schouten et al., 2018; Shiroyama et al., 2018; Tiu et al., 2018; Yoo et al., 2018) reported median follow-up times, which were <1 year in 13 studies (Calpe-Armero et al., 2017; Crinò et al., 2019; Fukui et al., 2019; Garassino et al., 2018; Grossi et al., 2018; Haratani et al., 2017; Kataoka et al., 2018; Ksienski et al., 2019; Sabatier et al., 2018; Sato et al., 2018; Schouten et al., 2018; Tiu et al., 2018;

Yoo et al., 2018) and ≥1 year in six studies (Costantini et al., 2018; Dudnik et al., 2018; Facchinetti et al., 2018; Lesueur et al., 2018; Schmid et al., 2018; Shiroyama et al., 2018). Median PFS ranged from 1.0 (Yoo et al., 2018) to 6.3 months (Tiu et al., 2018) in studies with median follow-ups of ≥1 year.

Thirty studies were case-series and three were cohort studies (Calpe-Armero et al., 2017; Ksienski et al., 2019; Yoo et al., 2018). Among case-series, the median PFS ranged from 1.5 (Haratani et al., 2017) to 6.3 months (Tiu et al., 2018). Among cohort studies, Ksienski et al. reported median PFS of 5.7 months (95% CI: 4.1–8.8) and 13.5 months (95% CI: 8.2–NR) for nivolumab and pembrolizumab, respectively (Ksienski et al., 2019). Calpe-Armero et al. reported median PFS of 2.76 months (95% CI: 1.28–9.87) for nivolumab and 2.0 months (95% CI: 1.58– 2.50) for docetaxel (Calpe-Armero et al., 2017). Yoo et al. reported median PFS of 1.1 months (95% CI: 0.8–3.0) for the overall sample, 1.0 months (95% CI: 0.6–1.7) for patients who received the standard dose of nivolumab, and 3.0 months (95% CI: 0.8–NR) for patients who received lower doses of nivolumab (Yoo et al., 2018).

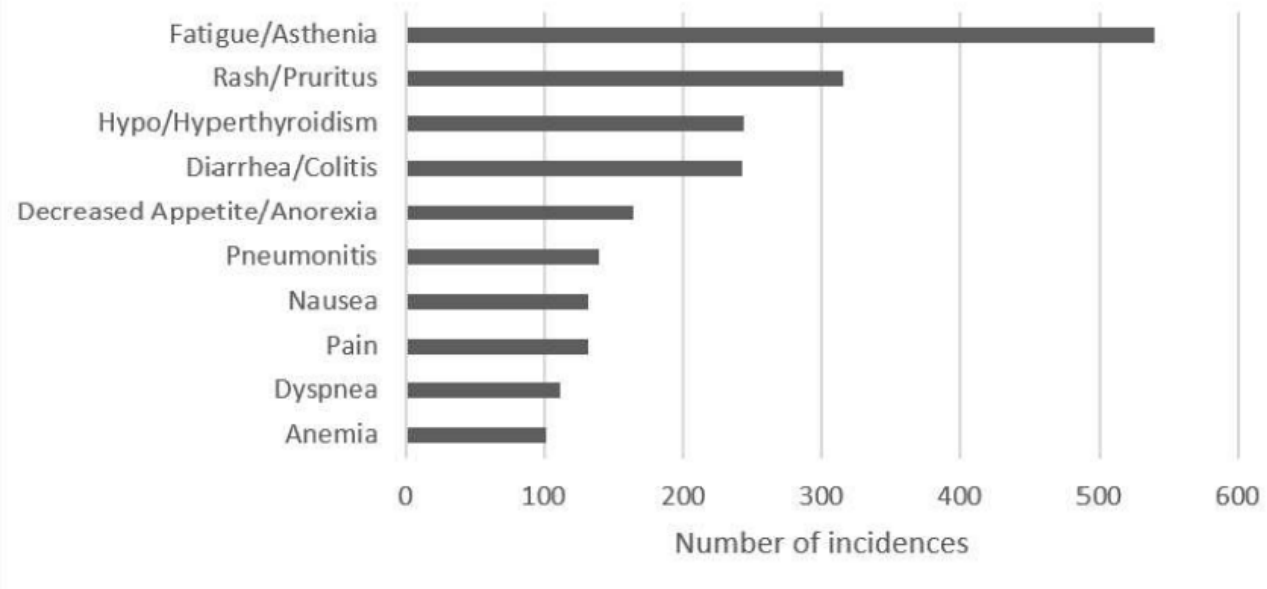
No statistically significant differences were observed among studies reporting median PFS for nivolumab stratified by age, sex, histology and brain metastasis (Appendix D). Statistically significant differences in median PFS were observed in subgroups defined by ECOG-PS. Four studies reported median PFS stratified by ECOG-PS, with higher ECOG-PS having negative association with median PFS (Dumenil et al., 2018; Merino Almazán et al., 2019; Montana et al., 2019; Schouten et al., 2018). The median PFS ranged from 2.3 (Montana et al., 2019) to 7.6 months (Merino Almazán et al., 2019) for ECOG-PS of 0–1, and 1.1 (Dumenil et al., 2018) to 2.1 months (Schouten et al., 2018) for ECOG-PS of ≥2. Seven studies reported aHRs comparing ECOG-PS of ≥2 with ECOG-PS of <2 (Bagley et al., 2017; Diem et al., 2017; Dumenil et al., 2018; Kataoka et

al., 2018; Lesueur et al., 2018; Schouten et al., 2018; Shiroyama et al., 2018); ECOG-PS was statistically significant in four studies (Dumenil et al., 2018; Kataoka et al., 2018; Lesueur et al., 2018; Shiroyama et al., 2018) with aHRs ranging from 1.60 (95% CI: 1.10–2.33) (Shiroyama et al., 2018) to 5.17 (95% CI: 1.99–13.43) (Dumenil et al., 2018).

3.4.5. Safety

Twenty-two studies reported information on treatment-related adverse events (TRAEs) (Areses Manrique et al., 2018; Bagley et al., 2017; Brustugun et al., 2017; Crinò et al., 2019; Dudnik et al., 2018; Dumenil et al., 2018; Fukui et al., 2019; Garassino et al., 2018; Garde-Noguera et al., 2018; Kobayashi et al., 2018; Ksienski et al., 2019; Lesueur et al., 2018; Merino Almazán et al., 2019; Montana et al., 2019; Sabatier et al., 2018; Sato et al., 2018; Schouten et al., 2018; Sekine et al., 2018; Shamai & Merimsky, 2018; Takeda et al., 2018; Tiu et al., 2018; Tournoy et al., 2018). A total of 2679 (58.4%) of all 4585 patients enrolled in the 22 studies experienced TRAEs of any grade; grade 3 and 4 TRAEs were reported in 440 (10.0%) patients (Areses Manrique et al., 2018; Bagley et al., 2017; Brustugun et al., 2017; Crinò et al., 2019; Dudnik et al., 2018; Dumenil et al., 2018; Fukui et al., 2019; Garassino et al., 2018; Garde-Noguera et al., 2018; Grossi et al., 2018; Kobayashi et al., 2018; Ksienski et al., 2019; Lesueur et al., 2018; Merino Almazán et al., 2019; Montana et al., 2019; Sabatier et al., 2018; Sato et al., 2018; Schouten et al., 2018; Tiu et al., 2018; Tournoy et al., 2018). The most common TRAEs associated with nivolumab were fatigue/asthenia (reported in 11.8% of the 4585 patients), rash/pruritis (6.9%), hypothyroidism/hyperthyroidism (5.3%), diarrhea/colitis (5.3%) and decreased appetite/anorexia (3.6%; Figure 5). The most common ≥grade 3 TRAEs were fatigue/asthenia (1.5%), pneumonitis (1.4%), diarrhea/colitis (0.9%), rash/pruritis (0.8%) and decreased appetite/anorexia (0.7%).

Figure 5 Incidence of most common treatment-related adverse events associated with nivolumab

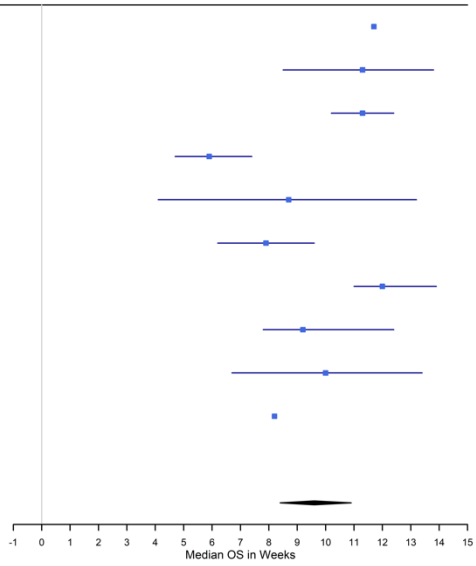


3.4.6. Meta-analysis of OS

Ten studies were included in the meta-analysis for OS (Brustugun et al., 2017; Costantini et al., 2018; Crinò et al., 2019; Dudnik et al., 2018; Fiorica et al., 2018; Grossi et al., 2018; Juergens et al., 2018; Ksienski et al., 2019; Schouten et al., 2018; Yoo et al., 2018). The pooled estimate showed that nivolumab was associated with a median OS of 9.6 months (95% CI: 8.4–10.9; $p < 0.0001$) (Figure 6). Heterogeneity across the studies was high ($I2 = 98\%$; $p < 0.0001$).

Figure 6 Pooled analysis of overall survival associated with nivolumab

Study	Sample Size	Median OS (Months)	95% CI
Brustugun et al.	58	11.7	Not Reported
Costantini et al.	303	11.3	8.5, 13.8
Crino et al.	1588	11.3	10.2, 12.4
Dudnik et al.	260	5.9	4.7, 7.4
Fiorica et al.	35	8.7	4.1, 13.2
Grossi et al.	371	7.9	6.2, 9.6
Juergens et al.	472	12.0	11.0, 13.9
Ksienski et al.	230	9.2	7.8, 12.4
Schouten et al.	248	10.0	6.7, 13.4
Yoo et al.	29	8.2	Not Reported
Summary Median		**9.6**	**8.4, 10.9**



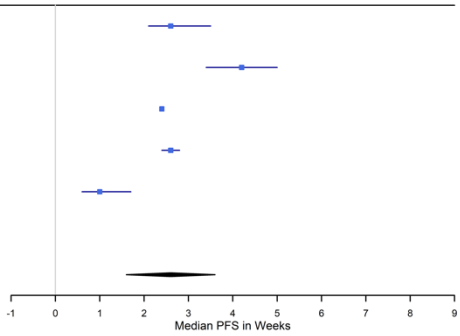
CI=confidence interval; OS=overall survival.

3.4.7. Meta-analysis of PFS

Five studies were included in the meta-analysis for PFS (Costantini et al., 2018; Grossi et al., 2018; Kataoka et al., 2018; Schouten et al., 2018; Yoo et al., 2018). The pooled estimate showed that nivolumab was associated with a median PFS of 2.6 months (95% CI: 1.6–3.6; $p < 0.0001$); (Figure 7). Heterogeneity across the studies was high ($I2 = 97\%$; $p < 0.0001$).

Figure 7 Pooled analysis of progression-free survival associated with nivolumab

Study	Sample Size	Median PFS (Months)	95% CI
Costantini et al.	303	2.6	2.1, 3.5
Grossi et al.	371	4.2	3.4, 5.0
Kataoka et al.	189	2.4	Not Reported
Schouten et al.	248	2.6	2.4, 2.8
Yoo et al.	29	1.0	0.6, 1.7
Summary Median		**2.6**	**1.6, 3.6**



CI=confidence interval; PFS=progression-free survival.

3.4.8. Publication Bias

Visual inspection of the funnel plot for OS suggests that publication bias is present (Appendix E). The asymmetry of the funnel plot suggests that smaller studies with lower OS are not being published.

3.4.9. GRADE

Overall evidence was assessed using the GRADE approach for both OS and PFS (Dijkers, 2013). The certainty of evidence was very low for both OS and PFS because of the observational nature of the included studies and inconsistency (Appendix F).

3.5. Discussion

ICIs targeting the PD-1/PD-L1 pathway are possible alternatives to docetaxel as means of treating advanced/metastatic NSCLC in second-line settings. Results from the CheckMate-017 and CheckMate-057 RCTs demonstrated that nivolumab was associated with longer median survival outcomes compared with docetaxel, and additional studies showed that treatment with nivolumab continued to yield positive results after 2–3-years of follow-up (Borghaei et al., 2015; Brahmer et al., 2015; Horn et al., 2017; Vokes et al., 2018). However, the effectiveness of nivolumab in real-

world settings, outside the domain of RCTs, remains unclear. Thus, we conducted this systematic review and meta-analysis to evaluate the effectiveness of nivolumab in real-world clinical practice settings, and to assess whether its effectiveness is comparable with the results seen in published RCTs.

Our meta-analysis indicated that nivolumab was associated with median OS and PFS of 9.6 and 2.6 months, respectively. The OS estimate fell below the median OS reported in the CheckMate-057 trial (12.2 months [95% CI: 9.7–15.0]) and EVIDENS study (11.2 months [95% CI: 10.0–12.4]), but it was higher than what was reported in the CheckMate-017 trial (9.2 months [95% CI: 7.3–13.3]). The PFS estimate from the meta-analysis was similar to the CheckMate-057 trial (2.3 months [95%CI: 2.2-3.3]) and EVIDENS study (2.8 months [95%CI: 2.6-3.2]); however, it was below the estimate reported in the CheckMate-017 trial (3.5 months [95%CI: 2.1-4.9]). Moreover, the OS and PFS estimates were comparable with the pooled results obtained from the CheckMate017 and CheckMate-057 trials; Vokes et al. reported pooled OS and PFS estimates of 11.1 and 2.56 months, respectively (Vokes et al., 2018). However, the certainty of the real-world evidence was very low, according to GRADE; therefore, future evidence may change the conclusions emerging from the current evidence about OS and PFS in real-world settings.

To the best of our knowledge, this was the first systematic review and meta-analysis conducted on nivolumab to assess its clinical effectiveness in real world settings. A strength of our meta-analysis was the use of the recently developed ‘meta-median’ package in R to obtain pooled summary estimates of median OS and PFS using study specific medians. Previously, these medians would be converted into means and standard errors for meta-analysis; however, the conversion assumed the outcome variables were normally distributed. Incorrect assumptions about the normality could introduce bias into meta-analyses using inverse variance weighting. McGrath and colleagues have

demonstrated that median-based meta-analyses performed better than conversion approaches (McGrath et al., 2020; McGrath et al., 2019).

Our review had several limitations. First, the meta-analysis included aggregate data from published articles, and no individual patient data, which may have increased the level of statistical heterogeneity observed in the results. Heterogeneity may have also resulted from the different types of NSCLC evaluated in the included studies. Furthermore, the included articles did not uniformly report OS or PFS by strata of important potential effect modifiers such as age, smoking status, biomarker status, and ECOG-PS. Additionally, since PD-L1 level of expression is the only predictive biomarker for PD-1/PD-L1 inhibitors, we hoped to examine the association between PD-L1 expression status and OS/PFS; however, the lack of data on PD-L1 levels in the included articles prevented us from carrying out this analysis. Thus, results of the meta-analyses should be interpreted with caution and considered to be solely exploratory in nature.

3.6. Conclusion

Our results suggest that real-world outcomes associated with nivolumab are consistent with what was observed in published RCTs. However, additional, large-scale, multicenter studies of high-quality or Phase IV studies using healthcare administrative databases are needed to support our conclusions.

Chapter 4: Factors Affecting Treatment Selection and Overall Survival for First-Line EGFR-TKI Therapy in Non-Small-Cell Lung Cancer

4.1. Abstract

Aim: To investigate the factors associated with treatment selection and OS for first-line EGFR-TKIs therapy among patients with non-small-cell lung cancer. **Methods**: We conducted a retrospective cohort study of linked administrative health databases in Ontario, Canada. **Results**: A total of 1,011 patients received an EGFR-TKI as first-line therapy. Treatment selection and OS associated with these treatments were affected by age, sex, geographical residency, comorbidities, and different sites of metastasis. **Conclusion**: Though recent approval of osimertinib offers a potential new standard of care in the first-line setting, earlier generation TKIs are still used to preserve osimertinib as a treatment option for later use. Our findings may contribute to optimizing treatment sequencing of upfront use of first- and second-generation use of EGFR-TKIs in the first-line setting for the treatment of *EGFR* mutation-positive NSCLC.

4.2. Introduction

The epidemiology of lung cancer is specified in Chapter 2 of this thesis. Advancements in our understanding of cancer biology have allowed us to tailor treatment approaches based on patients' genetic profiles. Half of NSCLC cases are associated with known mutations and several actionable gene alterations have been identified for targeted treatment (Dearden et al., 2013; Greulich, 2010; Korpanty, 2012). *EGFR* has been one of the most prevailing targets for devising specific treatment algorithms for patients with NSCLC. Approximately 15% of NSCLC cases have an activating mutation in the EGFR genes in exon 18-21 (Graham et al., 2018). Those harboring *EGFR* mutations are eligible to receive EGFR-TKIs, which have been demonstrated to improve ORR and PFS

compared to conventional chemotherapy in first-line settings (Fukuoka et al., 2011; Han et al., 2012; Inoue et al., 2013; Maemondo et al., 2010; Mitsudomi et al., 2010; Rosell et al., 2012; Sequist et al., 2013; Wu et al., 2014; Wu et al., 2015; Yang et al., 2015; Yoshioka et al., 2019; Zhou et al., 2011, Zhou et al., 2015).

There are currently five EGFR-TKIs approved as first-line treatment for NSCLC in Canada, including the first-generation TKIs erlotinib (Tarceva; Hoffman-La Roche, Basel, Switzerland) and gefitinib (Iressa; AstraZeneca, London, UK), second-generation TKIs afatinib (Giotrif; Boehringer Ingelheim, Ingelheim, Germany) and dacomitinib (Vizimpro, Pfizer, New York, NY, USA), and third-generation TKI osimertinib (Tagrisso; AstraZeneca, London, UK).

Currently, a dearth of clinical evidence exists to suggest whether one EGFR-TKI should be chosen over another among first- and second-generation EGFR-TKIs in a first-line setting (Girard, 2019; Nan et al., 2017). This suggests multiple factors could affect treatment selection, though a delineation of these factors in the case of EGFR-TKIs has never been undertaken. Previous research has identified general factors related to prescribing decisions, e.g., treatment sequencing, evidence from clinical trials, safety/toxicity profiles associated with each agent, growing familiarity with new agents among practitioners, regional/institutional preference, reimbursement, and influence of pharmaceutical companies (Fleischman et al., 2016; Schumock et al., 2004), though the applicability of these factors to EGFR-TKIs is unknown.

While several randomized controlled trials (RCTs) and observational studies have estimated the efficacy/effectiveness of prognostic factor-guided EGFR-TKIs in advanced/metastatic *EGFR* mutation-positive NSCLC population (Chao, 2017; Fujiwara et al., 2018; Fukuoka et al., 2011; Han et al., 2012; Ho et al., 2019; Inoue et al., 2013; Ito et al., 2018; Li et al., 2019; Lin et al., 2019;

Maemondo et al., 2010; Mitsudomi et al., 2010; Perol et al., 2016; Rosell et al., 2012; Sequist et al., 2013; Tokaca, 2018; Wu et al., 2014; Wu et al., 2015; Yang et al., 2015; Zhou et al., 2011, Zhou et al., 2015), limited information is available on the longitudinal effects of EGFR-TKIs at the population-level. Furthermore, evidence regarding the comparative effectiveness of these EGFR-TKIs is inconsistent across the literature.

To our knowledge, no studies thus far have investigated how prescribing decisions for EGFR-TKIs are made and the factors that may affect these prescribing decisions. Using population-based administrative health datasets, we sought to determine what factors influence the receipt of certain EGFR-TKIs in first-line settings and investigate how these are associated with overall survival. Due to the recency of the approval dates and concomitant lack of data for dacomitinib and osimertinib, the present study only pertained to afatinib, erlotinib, and gefitinib.

4.3. Methods

4.3.1. Study Design

This was a retrospective, population-based cohort study of linked health administrative data in Ontario, Canada. The datasets are housed at the Institute for Clinical Evaluative Sciences (ICES), a prescribed entity under Ontario's Personal Health Information Protection Act. The Act authorizes ICES to draw individual patient-level data from multiple health administrative datasets for researchers to use in secondary analyses. The research was cleared for ethics by the Office of Research Ethics at the University of Waterloo (ORE # 41067).

4.3.2. Study Population

The study included all patients diagnosed with NSCLC in Ontario between January 1, 2010 and August 31, 2019. NSCLC cases were identified through the Ontario Cancer Registry (OCR). The International Classification of Diseases for Oncology, Third Edition (ICD-O-3) site codes 34.0-34.9, in combination with relevant histology codes for non-squamous, squamous, and not otherwise specified (NOS) were used to identify cases of primary lung cancer from the OCR. Inclusion criteria were age ≥ 18 years at diagnosis, locally advanced or metastatic NSCLC, and receipt of afatinib, erlotinib, or gefitinib as first-line treatment. We excluded persons with death dates on or before the date of NSCLC diagnosis, and individuals who received more than one EGFR-TKI as first-line treatment. The dataset did not contain any information on biomarker status; thus, we assumed patients with records of EGFR-TKI prescription in the first-line setting had positive *EGFR* mutation status.

4.3.3. Data Sources

Multiple health administrative datasets were linked using encrypted unique identifiers. The OCR contains information on incident cancer cases and patients who have died of cancer in Ontario since 1964 (Clarke et al., 1991; Robles et al., 1988). The OCR includes data on date and stage of NSCLC diagnosis, age, sex, geographical location, rural versus urban residence, and date of death. The Registered Persons Database (RPDB) contains demographic information and vital statistics on all residents of Ontario who are eligible for universal healthcare coverage in the province. The Canadian Institute for Health Information – Discharge Abstract Database (CIHI-DAD) contains data on diagnoses and procedures for all in- and outpatient hospital admissions. The Ontario Drug Benefits (ODB) database contains data on all prescription medications dispensed to those eligible for publicly funded drug coverage. These include all persons aged ≥65 years, persons living in homes for special care and long-term care homes, persons receiving professional services through the home and community care service programs, persons receiving social assistance, and persons receiving benefits through Trillium Drug Program, a scheme which help people with high prescription drug costs relative to their net household income. The ODB does not capture information covered by private insurance and compassionate supplies from manufacturers. The Activity Level Reporting (ALR) system contains information on systemic and radiation therapy services and outpatient oncology clinic visits.

4.3.4. Covariates

We searched the literature and consulted expert opinion to identify several sociodemographic and clinical factors that may influence treatment selection and OS (Bergqvist et al., 2020; Booth et al., 2010; Charlson et al., 1987; Deyo et al., 1992; Girard, 2019; Hendriks et al., 2014; Kim et al., 2019; Lin et al., 2017; Schrijvers et al., 1997; Sorensen et al., 1988; Sperduto et al., 2017; Stavem et al.,

2017). These factors included: year of diagnosis, age, sex, rurality. neighborhood income quintile, Local Health Integration Network (LHIN), clinical stage, histology, Charlson-Deyo Comorbidity Index (CCI), and sites of metastasis (bone, brain, liver, lung).

Neighborhood household income was determined through linkage of postal codes to Canadian census data and stratified into three tertiles, with the first and last tertiles representing neighborhoods with the lowest and highest income status, respectively. CCI was determined from hospitalization data utilizing a two-year 'look-back' window, with the score from the most recently available hospitalization record applied to each participant (Charlson et al., 1987; Deyo et al., 1992). We followed Stavem et al's approach and considered missing comorbidities to be absent (Charlson et al., 1987; Deyo et al., 1992; Stavem et al., 2017). At the time of data collection, publicly funded healthcare services in Ontario were administered on a regional basis by 14 LHINs, each with its own distinct geographical territory. Recently, Ontario integrated these LHINS into five regions consisting of North, West, Toronto Central, East, and South regions. The analyses were conducted reflective of these changes.

4.3.5. Statistical Analysis

All variables were categorical and described using frequencies and percentages. To explore the factors associated with treatment selection, we conducted two separate logistic regression analyses comparing afatinib to gefitinib and erlotinib to gefitinib. We used gefitinib as the reference category because it was the most established treatment group among the three EGFR-TKIs; erlotinib and gefitinib have been in use since 2010, while afatinib was approved for use and publicly funded in 2014. Furthermore, while erlotinib is only publicly funded for second- and third-line settings in Ontario, it is indicated for first line setting as well. The aim of our models was not to predict treatment selection, but to identify which variables may be of importance to clinicians prescribing

EGFR-TKIs for first-line treatment. Therefore, our focus was not to identify the most parsimonious model, but rather to build an explanatory model and examine the effects of all relevant covariates on treatment selection.

A priori, we defined sociodemographic and clinical factors that may be important in clinical decision-making for treatment selection and its associated outcomes (see 'Covariates' above) (Bergqvist et al., 2020; Booth et al., 2010; Charlson et al., 1987; Deyo et al., 1992; Girard, 2019; Kim et al., 2019; Lin et al., 2017; Schrijvers et al., 1997). A series of chi-square tests were conducted to test the associations between independent variables and the outcome variable. In addition, all explanatory variables were checked for multicollinearity using variance inflation factors. Discrimination of the models was assessed with the area under the receiver operating characteristic curve (AUC). Calibration of the models was evaluated using the Hosmer Lemeshow goodness-of-fit tests.

OS was assessed using the Kaplan-Meier method on the overall population and various patient subgroups. The OS was calculated from the date of diagnosis of NSCLC to death (for any reason) or the last day of patient follow-up (censored). Comparisons between groups were performed using the log rank test. Multivariable Cox proportional hazards models were used to determine adjusted hazard ratios (aHR) and to evaluate the predictive factors for survival. Statistical significance was set at α=0.05. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC).

4.4. Results

88,179 patients were identified as having a primary diagnosis of lung cancer in the OCR between 2010 and 2019. Of these, 68,334 were NSCLC cases and 33,321 had stage IIIB/IV NSCLC. In total, 1011 patients met the eligibility criteria and were enrolled in the study (

Table 5); 67 patients were excluded as they had records of receiving more than one EGFR-TKI in the first-line setting (Figure 8). 110 (10.9%) patients received afatinib, while 482 (47.7%) and 419 (41.4%) received erlotinib and gefitinib, respectively. Male patients constituted 41.8% of the study population. Almost all patients had nonsquamous histology (98.7%) and no patients had squamous cell carcinoma. The majority of patients were at stage IV NSCLC (89.8%) at the time of diagnosis.

Figure 8 Flow Diagram of Sample Attrition

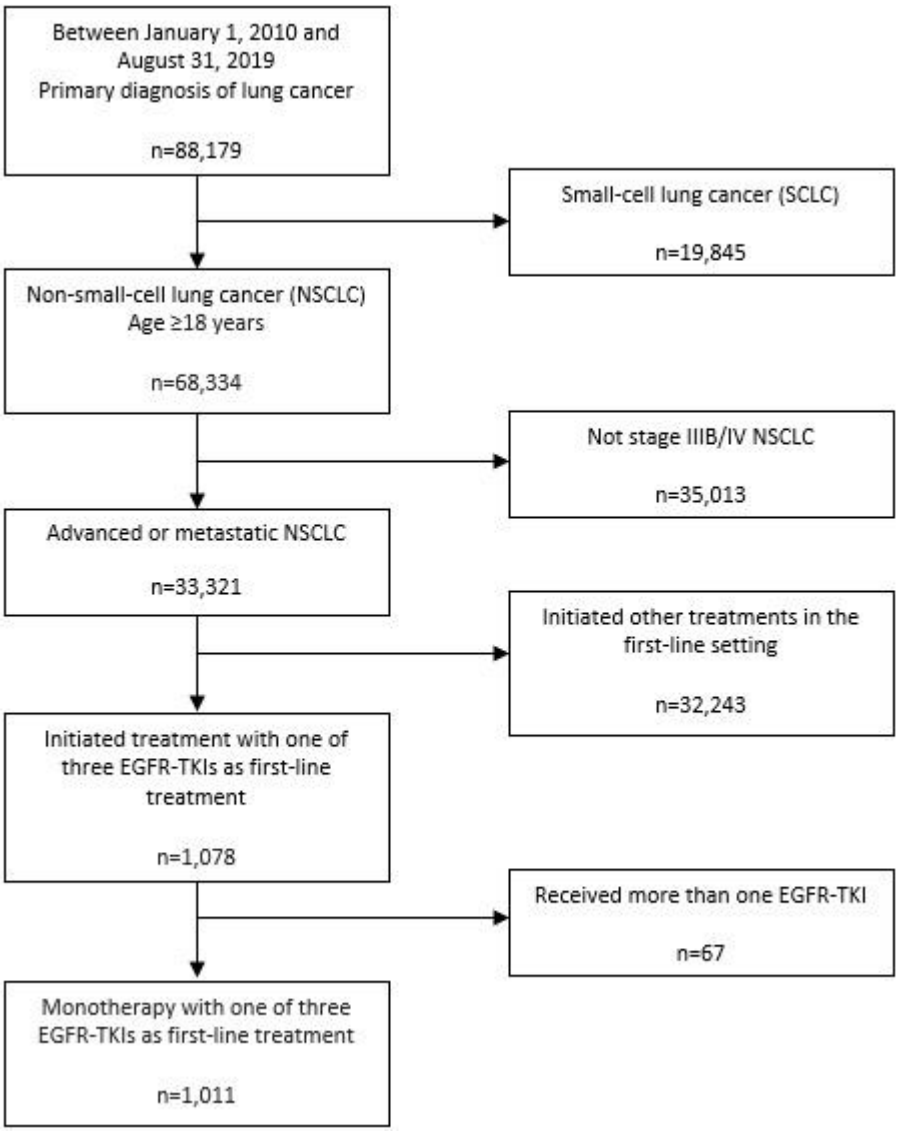


Table 5 Table 1. Baseline patient sociodemographic and clinical characteristics

	Afatinib	Erlotinib	Gefitinib	Total	P-value
	n = 110 (%)	n = 482 (%)	n = 419 (%)	n = 1011 (%)	
Year of Diagnosis					<.0001
2010-2014	6 (5.4%)	425 (88.2%)	178 (42.5%)	609 (60.2%)	
2015-2019	104 (94.6%)	57 (11.8%)	241 (57.5%)	402 (39.8%)	
Age, years					<.0001
18-59	36 (32.7%)	126 (26.1%)	84 (20.1%)	246 (24.3%)	
60-69	15 (13.6%)	85 (17.6%)	53 (12.7%)	153 (15.1%)	
70-79	55 (50.0%)	247 (51.3%)	217 (51.8%)	519 (51.3%)	
80+	4 (3.6%)	24 (5.0%)	65 (15.5%)	93 (9.2%)	
Sex					<.0001
Male	44 (40.0%)	245 (50.8%)	134 (32.0%)	423 (41.8%)	
Female	66 (60.0%)	237 (49.2%)	285 (68.0%)	588 (58.2%)	
Rurality					0.20
Rural	15 (13.6%)	65 (13.5%)	41 (9.8%)	121 (12.0%)	
Urban	95 (86.4%)	417 (86.5%)	378 (90.2%)	890 (88.0%)	
Neighborhood Income Quintile					0.27
1 (poorest)	57 (51.8%)	208 (43.2%)	167 (39.9%)	432 (42.7%)	
2	16 (14.6%)	86 (17.8%)	78 (18.6%)	180 (17.8%)	
3 (wealthiest)	37 (33.6%)	188 (39.0%)	174 (41.5%)	399 (39.5%)	
Local Health Integration Network (LHIN)					<.0001
North	11 (10.3%)	30 (6.3%)	17 (4.1%)	58 (5.8%)	
West	27 (25.2%)	150 (31.4%)	84 (20.4%)	261 (26.2%)	
Toronto	9 (8.4%)	33 (6.9%)	55 (13.3%)	97 (9.7%)	
Central	34 (31.8%)	89 (18.6%)	168 (40.8%)	291 (29.2%)	
East	26 (24.3%)	176 (36.8%)	88 (21.4%)	290 (29.1%)	
Clinical Stage					0.06
IIIB	11 (10.0%)	60 (12.4%)	32 (7.6%)	103 (10.2%)	
IV	99 (90.0%)	422 (87.6%)	387 (92.4%)	908 (89.8%)	
Histology					0.33
Non-squamous	109 (99.1%)	478 (99.2%)	411 (98.1%)	998 (98.7%)	
Squamous Cell	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
NOS	1 (0.9%)	4 (0.8%)	8 (1.9%)	13 (1.3%)	
Charlson Co-morbidity Index (CCI)					0.25
No	107 (97.3%)	452 (93.8%)	400 (95.5%)	959 (94.9%)	
Yes	3 (2.7%)	30 (6.2%)	19 (4.5%)	52 (5.1%)	
Sites of Metastasis					
Liver	16 (14.6%)	66 (13.7%)	44 (10.5%)	126 (12.5%)	0.27
Bone	40 (36.4%)	150 (31.1%)	167 (39.9%)	357 (35.3%)	0.02
Brain	26 (23.6%)	66 (13.7%)	98 (23.4%)	190 (18.8%)	0.0004
Lung	19 (17.3%)	121 (25.1%)	101 (24.1%)	241 (23.8%)	0.22

4.4.1. Treatment Selection

The results of the logistic regression analyses are presented in Table 6. We found no evidence of multicollinearity between explanatory variables. The goodness-of-fit of the models were confirmed (Hosmer-Lemeshow: Chi-square = 7.29 and p = 0.50 for gefitinib versus erlotinib; chi-square = 8.33 and p = 0.40 for gefitinib versus afatinib) and the models exhibited moderate discriminatory capacity (AUC = 0.75 for gefitinib versus erlotinib; AUC = 0.69 for gefitinib versus afatinib).

Age was associated with prescribing choice of EGFR-TKIs, with older patients more likely to be prescribed gefitinib over afatinib and erlotinib. Compared to patients aged 18-59 years, the adjusted odds ratio (aOR) for prescribing afatinib in lieu of gefitinib in patients aged ≥80 years was 0.14 (95%CI: 0.04- 0.42), and 0.19 (95%CI: 0.10-0.34) for erlotinib versus gefitinib. A larger proportion of patients aged ≥70 years received gefitinib over the other two drugs. Erlotinib was more commonly prescribed for male patients compared to gefitinib (aOR: 2.59; 95%CI: 1.90-3.52). Regional prescribing preferences were evident. Patients residing in LHIN – North region, compared to Toronto Central, were less likely to be prescribed gefitinib over afatinib and erlotinib. The adjusted odds of receiving afatinib was 3.30 (95%CI: 1.02-10.64) times greater than receiving gefitinib, while it was 2.57 (95%CI: 1.15-5.75) times greater for erlotinib versus gefitinib. In the West and East regions, erlotinib was more commonly prescribed over afatinib and gefitinib. The adjusted odds of being prescribed erlotinib in the West region was 2.94 (95%CI: 1.68-5.14) and 3.51 (95%CI: 2.01-6.11) in the East region.

We found associations between sites of metastasis and prescribing decisions. Patients with metastasis to bone and brain were less likely to be prescribed erlotinib compared to gefitinib. Among patients with bone metastasis, the aOR for erlotinib prescription was 0.58 (95%CI: 0.42-

0.80), while it was 0.53 (95%CI: 0.36-0.78) for patients with brain metastasis. However, erlotinib was more commonly prescribed for patients with liver metastasis compared to gefitinib, with an aOR of 1.74 (95%CI: 1.10- 2.78).

Table 6 Adjusted odds ratios for prescription of afatinib and erlotinib compared to gefitinib

Variable	Afatinib, OR (95% CI)	Erlotinib, OR (95% CI)	Gefitinib (Reference)
N=	110	482	419
Age, years			
18-59	1	1	1
60-69	0.83 (0.40-1.73)	1.12 (0.69-1.83)	1
70-79	0.66 (0.39-1.12)	0.73 (0.50-1.06)	1
80+	0.14 (0.04-0.42)	0.19 (0.10-0.34)	1
Sex			
Male	1.43 (0.89-2.27)	2.59 (1.90-3.52)	1
Female	1	1	1
Rurality			
Rural	1.10 (0.52-2.31)	0.98 (0.60-1.59)	1
Urban	1	1	1
Neighborhood Income Quintile			
1 (poorest)	1.53 (0.78-2.97)	1.07 (0.71-1.63)	1
2	1	1	1
3 (wealthiest)	0.94 (0.47-1.87)	0.98 (0.64-1.48)	1
LHIN			
North	3.30 (1.02-10.64)	2.57 (1.15-5.75)	1
West	2.03 (0.86-4.82)	2.94 (1.68-5.14)	1
Toronto	1	1	1
Central	1.03 (0.45-2.34)	0.73 (0.42-1.26)	1
East	1.66 (0.70-3.95)	3.51 (2.01-6.11)	1
Clinical Stage			
IIIB	1.70 (0.75-3.85)	1.43 (0.84-2.44)	1
IV	1	1	1
Charlson Comorbidity Index			
No	1.58 (0.44-5.68)	0.81 (0.42-1.59)	1
Yes	1	1	1
Bone Metastasis			
Yes	0.78 (0.47-1.29)	0.58 (0.42-0.80)	1
No/Unknown	1	1	1

Variable	Afatinib, OR (95% CI)	Erlotinib, OR (95% CI)	Gefitinib (Reference)
Liver Metastasis			
Yes	1.58 (0.78-3.20)	1.74 (1.10-2.78)	1
No/Unknown	1	1	1
Brain Metastasis			
Yes	1.14 (0.67-1.97)	0.53 (0.36-0.78)	1
No/Unknown	1	1	1
Lung Metastasis			
Yes	0.64 (0.36-1.16)	1.37 (0.96-1.95)	1
No/Unknown	1	1	1

CI – Confidence Interval; OR – Odds Ratio; LHIN – Local Health Integration Network;

4.4.2. Survival Analysis

The median OS of the overall cohort was 19.53 months (95%CI: 18.38-20.75) (Figure 9). Statistically significant differences in OS were observed across the EGFR-TKIs; the median OS were 31.04 months (95%CI: 23.41-42.05), 17.36 months (95%CI: 16.04-18.48), and 21.63 months (95%CI: 19.27-23.18) for afatinib, erlotinib, and gefitinib, respectively (Figure 10a). Significantly shorter OS was observed for patients who were male (median: 17.33 months, 95%CI: 16.01-18.97, p-value for log-rank test = 0.0017, Figure 10c), had presence of comorbidities (15.81 months, 95%CI: 13.32-20.52, p-value for log-rank test = 0.026, Figure 10h), and had metastasis to liver (16.27 months, 95% CI: 14.14-18.44, p-value for log-rank test = 0.0001, Figure 10i) and bone (17.98 months, 95%CI: 16.21-20.38, p-value for log-rank test = 0.0094, Figure 10j). Furthermore, shorter median OS was observed among older patients, but the difference was not statistically significant.

Figure 9 Overall survival for the entire study population

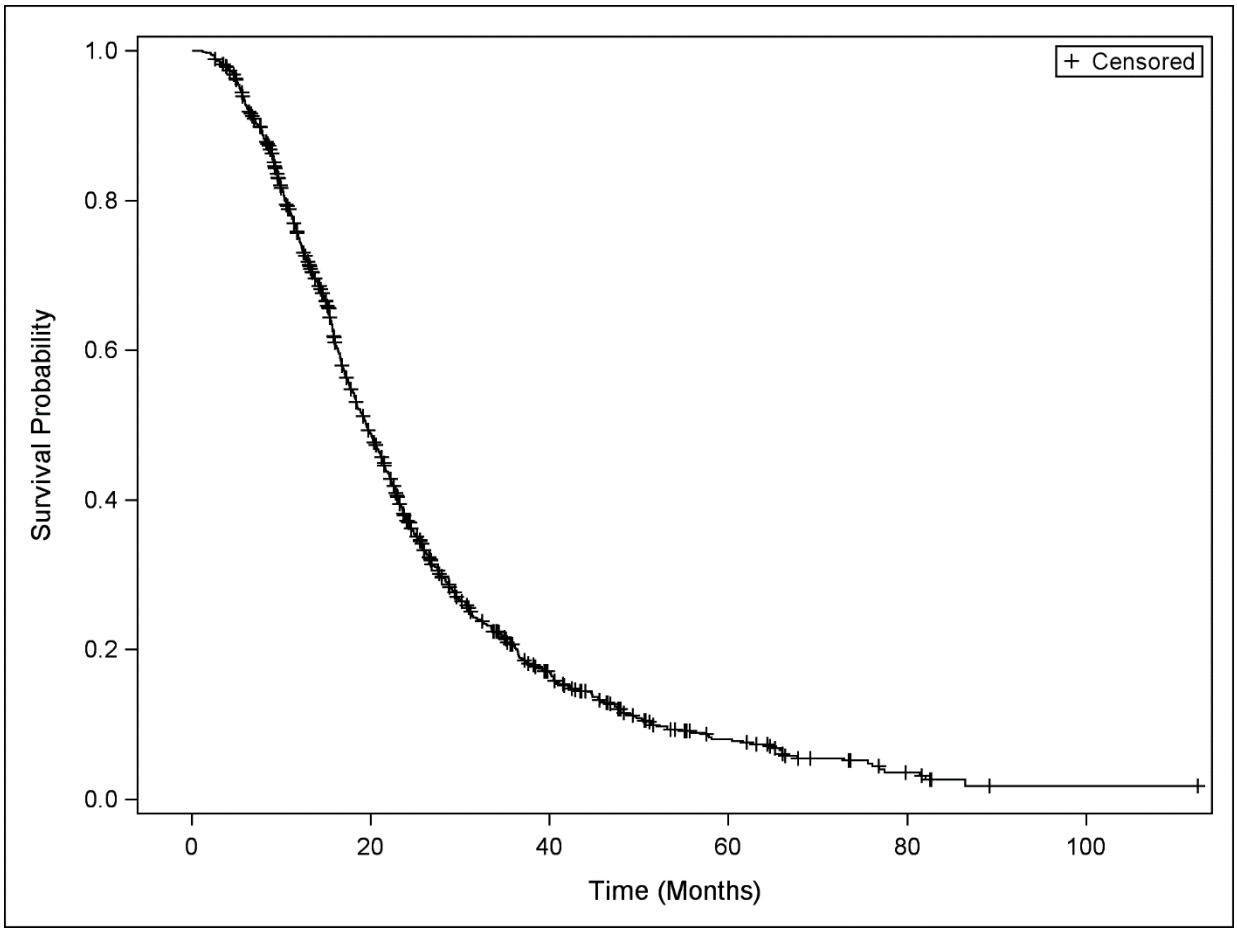
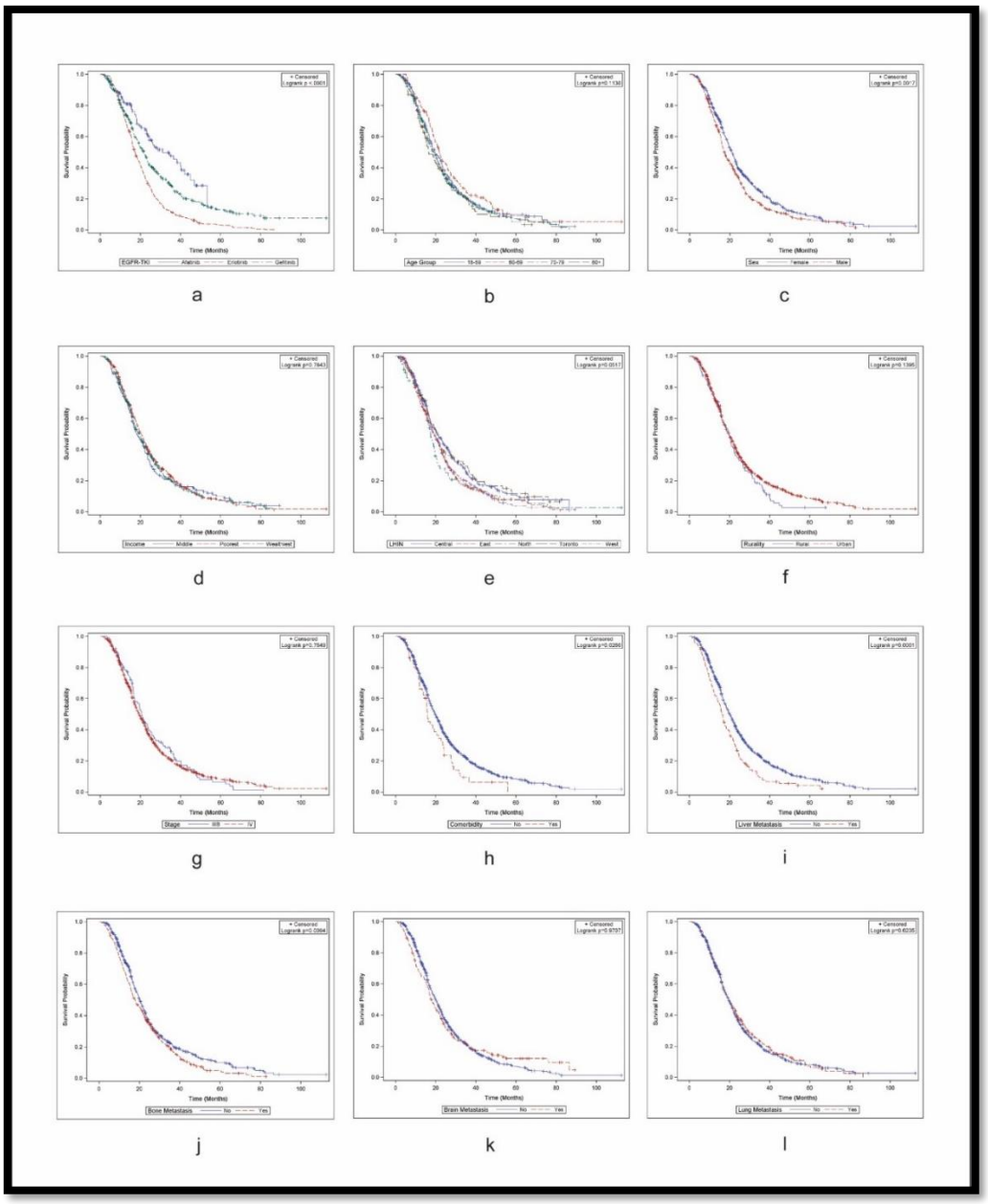


Figure 10 Overall survival by patient factors



Overall survival according to treatment (afatinib, erlotinib, or gefitinib) **(A)**; age groups **(B)**; sex **(C)**; income **(D)**; geographical residency **(E)**; rural vs. urban **(F)**; clinical stage **(G)**; presence of comorbidity **(H)**; liver metastasis **(I)**; bone metastasis **(J)**; brain metastasis **(K)**; and lung metastasis **(L)**

A multivariable Cox regression model showed that prescription of erlotinib (aHR: 1.58, 95%CI: 1.33-1.86, p< .0001), age 80+ (aHR: 1.42, 95%CI: 1.07-1.88, p=0.02), presence of comorbidities (aHR: 1.37, 95%CI: 1.01-1.86, p=0.04), liver metastasis (aHR: 1.49, 95%CI: 1.22-1.83, p=.0001), bone metastasis (aHR: 1.31, 95%CI: 1.13-1.53, p=0.0004), and brain metastasis (aHR: 1.30, 95%CI: 1.07-1.57, p=0.007) were inversely associated with OS (Table 3). Prescription of afatinib (aHR: 0.61, 95%CI: 0.45-0.82, p=0.0013) was positively associated with OS (Table 7).

Table 7 Multivariable Cox regression of overall survival

Variable	HR (95% CI)	P-value
EGFR-TKI		
Afatinib	0.61 (0.45-0.82)	0.0013
Erlotinib	1.58 (1.33-1.86)	<.0001
Gefitinib	Ref	
Age		
18-59	Ref	
60-69	0.86 (0.68-1.08)	0.18
70-79	1.15 (0.96-1.37)	0.13
80+	1.42 (1.07-1.88)	0.02
Sex		
Male	1.14 (0.99-1.32)	0.08
Female	Ref	
Rurality		
Urban	Ref	
Rural	1.05 (0.84-1.30)	0.67
Clinical Stage		
IIIB	1.05 (0.83-1.34)	0.68
IV	Ref	
Charlson Co-morbidity Index		
No	Ref	
Yes	1.37 (1.01-1.86)	0.04
Income		
Poorest	Ref	
Middle	1.09 (0.90-1.32)	0.40
Wealthiest	1.04 (0.89-1.21)	0.67
LHIN		
North	1.35 (0.92-1.97)	0.12
West	1.13 (0.86-1.48)	0.40
Toronto	Ref	
Central	1.05 (0.81-1.37)	0.72

Variable	HR (95% CI)	P-value
East	1.15 (0.88-1.50)	0.30
Liver Metastasis		
No	Ref	
Yes	1.49 (1.22-1.83)	0.0001
Bone Metastasis		
No	Ref	
Yes	1.31 (1.13-1.53)	0.0004
Brain Metastasis		
No	Ref	
Yes	1.30 (1.07-1.57)	0.007
Lung Metastasis		
No	Ref	
Yes	0.94 (0.80-1.11)	0.48

HR – Hazards Ratio; CI – Confidence Interval; LHIN – Local Health Integration Network; Ref – Reference

4.5. Discussion

We identified sociodemographic and clinical factors influencing treatment selection and OS among patients who received EGFR-TKIs between 2010-2019. Compared to gefitinib, erlotinib was prescribed more frequently for those who were males, residing in certain geographical locations (North, West, and East regions), and had liver metastasis. The results for afatinib were similar, while a higher prescription of afatinib was noted among patients with no comorbidities and who had brain metastasis, although the results were not statistically significant. Compared with afatinib and erlotinib, gefitinib was more commonly prescribed for older patients and those with bone metastasis. Meanwhile, it was found that type of EGFR-TKI therapy, age, presence of comorbidities, and metastasis to liver, bone, and brain could be independent prognostic factors for OS.

We expected to find some of the associations reported in Tables 2 and 3. In terms of the use of gefitinib for patients with bone metastasis, previous studies suggested that gefitinib may reduce bone metastasis growth through inhibition of EGF signaling pathways in bone stromal cells and

improve pathologic fractures (Lu et al., 2009; Okano & Nishio, 2008). Furthermore, the high usage of gefitinib in older patients may partly be explained by the safety/toxicity profile of afatinib compared to erlotinib or gefitinib. While results from the noninterventional RealGiDo study indicated that AEs with afatinib can be managed with dose adjustments and care measures (Halmos et al., 2019), older patients may not be able to handle the intensity of AEs associated with afatinib. For patients with terminal NSCLC, the intent of treatment would likely focus on health-related quality of life, which involves minimizing treatment related AEs and managing symptoms.

Another factor to consider is acquired resistance, the most common being the development of a T790M mutation, which occurs in 50%-70% of cases (Arcila et al., 2011; Sequist et al., 2011; Yang et al., 2017). Studies have shown that afatinib is able to overcome acquired first-generation EGFR-TKI resistance (Heigener & Reck, 2011; Heigener et al., 2015). While afatinib is not publicly funded for second-line settings in Ontario, funding of afatinib for patients who have initiated another EGFR-TKI therapy in the first line setting, and who have not had disease progression, are considered on a case-by-case basis.

Our median OS estimate stratified by EGFR-TKIs are inconsistent with what has been reported in several trials (Fukuoka et al., 2011; Han et al., 2012; Inoue et al., 2013; Maemondo et al., 2010; Mitsudomi et al., 2010; Rosell et al., 2012; Sequist et al., 2013; Wu et al., 2015; Yang et al., 2015; Yoshioka et al., 2019; Zhou et al., 2011, Zhou et al., 2015). The median OS observed in our study for erlotinib and gefitinib were shorter than what was observed in most published trials. Exception was the results reported in the IPASS trial, where median OS was 18.8 months for gefitinib (Fukuoka et al., 2011). However, the median OS of afatinib observed in our study was longer than what was reported in phase IIb LUX-Lung 7 trial (27.9 months) and phase III LUX-Lung 3 (28.2 months) and LUX-Lung 6 (23.1 months) trials (Han et al., 2012; Park et al., 2016; Yang et al.,

2015). The differences in median OS between EGFR-TKIs was consistent with other observational studies that reported effectiveness of EGFR-TKIs in clinical practice (Bergqvist et al., 2020; Chao, 2017; Clarke et al., 1991; Fujiwara et al., 2018; Ho et al., 2019; Ito et al., 2018; Li et al., 2019; Lin et al., 2019; Perol et al., 2016; Robles et al., 1988; Tokaca, 2018). Most studies reported higher median OS associated with afatinib compared to erlotinib or gefitinib (Fujiwara et al., 2018; Ito et al., 2018; Lin et al., 2019). However, Li and colleagues reported higher median OS observed in patients receiving erlotinib (23.2 months) compared to afatinib (20.7 months) (Lin et al., 2019). In addition, Chao and colleagues reported substantially higher median OS for patients receiving erlotinib (34.6 months) compared to those receiving gefitinib (19.2 months) (Chao, 2017).

Given the fact that 15% of patients with non-squamous histology whose tumor harbor *EGFR* mutation, we had expected a larger sample for our study. However, the relatively small sample size could be attributed to the initial challenges of implementing biomarker testing in Ontario in the early 2010s, along with logistical difficulties, e.g., delayed turnaround times, which led chemotherapy to be used as the first-line treatment to avoid clinical deterioration (Cheema et al., 2017; Ellis et al., 2013). A previous study has suggested that approximately 1 in 4 patients do not undergo biomarker testing (Spicer, 2015). Furthermore, the ODB database captured only information related to publicly funded medications; therefore, prescription medications covered by private insurance and compassionate supplies from manufacturers could not be considered.

We found that 38.9% of our study cohort initiated a second line therapy, which questions the notion of reserving therapies for subsequent use (e.g. development of acquired T790M mutation resistance) to maximize the duration of chemotherapy-free treatment. The results from the phase III FLAURA trial demonstrated superior efficacy and safety profiles associated with osimertinib compared to first-generation TKIs in the first-line setting, regardless of T790M mutational status (Soria et al.,

2018). In terms of treatment sequencing, patients receiving osimertinib as first-line treatment would not receive any subsequent EGFR-TKIs upon progression and would likely involve treatment with platinum doublet. Therefore, clinical challenges remain in deciding whether the most effective therapy should be used as first-line treatment or be reserved for later lines to expand treatment options.

A strength of our study was the linkage and use of population-based administrative datasets, which captured all relevant data and complete follow-up for all patients. To our knowledge, this was the first study to systematically assess the factors influencing prescribing decisions associated with EGFR-TKIs using administrative datasets.

Nonetheless, our study has limitations. First, the number of patients who received afatinib was relatively small compared to patients who received erlotinib and gefitinib, due to later approval of afatinib. The difference in sample size resulting from the late licensing date may have contributed to selection and length-time bias in our study, which may have caused overestimation of odds ratios and survival estimates in our analyses. The overall survival data for persons who received erlotinib and gefitinib were more mature compared to persons who received afatinib. In addition, previous studies have demonstrated the importance of ECOG-PS and the type of *EGFR* mutation status, e.g., exon 19 deletion (Exon19DEL) and the exon 21 codon 858 point mutation (L858R), as important factors to consider in treatment selection and survival (Cha et al., 2015; Hung et al., 2018; Jackman et al., 2006; Pirker et al., 2012; Ren et al., 2014; Riely et al., 2006; Tu et al., 2017; Yang et al., 2015). However, a lack of data on ECOG-PS and *EGFR* mutation status prohibited us from carrying out any analyses involving these factors. We assumed that patients who received any of the three EGFR-TKI had positive *EGFR* mutation, regardless of the type. Although highly unlikely, we cannot rule out the possibility that TKIs may have been prescribed to EGFR wild-type patients.

Lastly, since the ODB database did not capture information on private insurance claims and compassionate supplies, we were not able to assess prescribing differences based on types of insurance.

4.6. Conclusion

The results of the present study demonstrated that factors such as age, sex, geographical residency, and metastasis to bone, liver, and brain were independent factors influencing treatment selection of EGFR-TKIs. Presence of comorbidities, in addition to the aforementioned factors, were independent prognostic factors for OS. In clinical practice, there were significant differences in overall survival between the three EGFR-TKIs. Additional population-based studies are required to compare the clinical effectiveness of EGFR-TKIs stratified by *EGFR* mutation status.

Chapter 5: Cost-Effectiveness Analysis of Afatinib, Erlotinib, and Gefitinib as First-Line Treatment for EGFR Mutation-Positive Non-Small-Cell Lung Cancer in Ontario, Canada

5.1. Abstract

Objective: The objective of this study was to compare the cost effectiveness of first-line epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) for the treatment of non-small-cell lung cancer. **Methods:** This study used Ontario Cancer Registry-linked administrative data to identify patients with a primary diagnosis of lung cancer who received EGFR-TKIs as first-line treatment between 1 January, 2014 and 31 August, 2019. A net benefit regression approach accounting for baseline covariates and propensity scores was used to estimate incremental net benefits and incremental cost-effectiveness ratios. Outcome measures were calculated over a 68-month period and were discounted with an annual rate of 1.5%. Sensitivity analyses were conducted to assess and characterize the uncertainties. **Results:** A total of 547 patients were included in the study, of whom 20.1%, 23.6%, and 56.3% received afatinib, erlotinib, and gefitinib, respectively. Erlotinib was dominated by afatinib and gefitinib. Compared to gefitinib, afatinib was associated with higher effectiveness (adjusted incremental quality-adjusted life-year: 0.21), higher total costs (adjusted incremental costs: $9745), and an incremental cost-effectiveness ratio of $46,506 per quality-adjusted life-year gained. Results from the sensitivity analyses indicated the findings of the base-case analysis were robust. **Conclusions:** Contrary to previously published studies, our study established head-to-head comparisons of effectiveness and treatment-related costs of first-line EGFR-TKIs. Our findings suggest afatinib was the most cost-effective option among the three EGFR-TKIs.

5.2. Introduction

The epidemiology of lung cancer is specified in Chapter 2 of this thesis. Roughly half of all NSCLC cases are associated with known genetic mutations, 15% of which are linked to an activating mutation in the EGFR genes (Graham et al., 2018). TKIs of the *EGFR* have become the standard treatment for patients with advanced NSCLC harboring an *EGFR* mutation. Compared to conventional chemotherapy, EGFR-TKIs have shown improved ORR and PFS in first-line settings (Fukuoka et al., 2011; Han et al., 2012; Inoue et al., 2013; Maemondo et al., 2010; Mitsudomi et al., 2010; Rosell et al., 2012; Sequist et al., 2013; Wu et al., 2014; Wu et al., 2015; Yang et al., 2015; Yoshioka et al., 2019; Zhou et al., 2011, Zhou et al., 2015).

Recent approval of osimertinib offers a potential new standard of care in the first line setting for treatment of advanced or metastatic *EGFR* mutation-positive NSCLC (Mok et al., 2017; Soria et al., 2018). However, two popular treatment protocols for EGFR-TKIs currently exist; one involves front-line use of osimertinib, while the other involves front-line use of first- or second-generation EGFR-TKIs, followed by osimertinib as second-line salvage therapy for patients who progress and develop resistance through the T790M mutation (Girard, 2019). There is no concrete evidence to suggest one treatment protocol is superior to another, indicating earlier generation EGFR-TKIs (i.e., afatinib, erlotinib, and gefitinib) remain a mainstay of first-line treatment options in clinical practice.

Previous studies that compared the effectiveness and cost-effectiveness of first-line EGFR-TKIs generally used model-based analyses whereby parameterization of model inputs and assumptions were largely derived from randomized controlled trials (RCTs) (Arrieta et al., 2020; Chouaid et al., 2017; Gu et al., 2019; Lee et al., 2014; Ting et al., 2015; Yang et al., 2020). The use of model

analyses is associated with many limitations such as incorporation of model assumptions (e.g., Markovian assumption), restrictive inclusion and exclusion criteria, limited lengths of follow-up, extrapolation of observed survival data, and limited information on treatment-related healthcare costs. Furthermore, previous studies have used conventional chemotherapy as the comparator to infer effectiveness through indirect treatment comparisons across EGFR-TKIs (Gu et al., 2019; Ting et al., 2015). Hence, the use of real-world data to directly compare the effectiveness and cost-effectiveness of EGFR-TKIs may help inform or revise healthcare resource allocation decisions.

The aim of our study was to assess the comparative cost-effectiveness of three EGFR-TKIs – afatinib, erlotinib, and gefitinib – for first-line treatment of advanced and metastatic NSCLC using a large, population-based, person-level claims database from a healthcare payer perspective. The present study was limited to these three EGFR-TKIs due to the lack of real-world data and recent regulatory approval for dacomitinib and osimertinib.

5.3. Methods

5.3.1. Study Design

This was a retrospective cohort study of linked health administrative data in the province of Ontario, Canada. The datasets are housed at the ICES, a prescribed entity under Ontario's Personal Health Information Protection Act. The Act authorizes ICES to draw individual patient-level data from multiple health administrative datasets for researchers to use in secondary analyses. Our research was cleared for ethics by the Office of Research Ethics at the University of Waterloo (ORE # 41067).

5.3.2. Study Population

The study included all eligible NSCLC cases in Ontario between January 01, 2014 and August 31, 2019. The dates were chosen in alignment with the year afatinib became commercially available in Ontario to latest available data at time of analysis (gefitinib and erlotinib were available prior to 2014). We identified cases of primary lung cancer using the ICD-O-3 site codes 34.0-34.9, in combination with relevant histology codes for non-squamous, squamous, and not otherwise specified. Inclusion criteria were age ≥18 years at diagnosis, locally advanced or metastatic NSCLC, and records of receipt of afatinib, erlotinib, or gefitinib as first-line treatment. Persons with recorded death dates on or before the date of NSCLC diagnosis, and persons who had records of receipt of ≥1 EGFR-TKI in first-line settings were excluded from the study. Information on biomarker status was not available in the dataset and we therefore assumed patients with records of EGFR-TKI prescription in first-line settings had positive *EGFR* mutation status.

5.3.3. Data Sources

We linked multiple health administrative datasets using encrypted unique identifiers. NSCLC cases were identified through the OCR, which contains information on incident cancer cases and patients who have died of cancer in Ontario since 1964 (Clarke et al., 1991; Robles et al., 1988). The OCR includes data on date of diagnosis, stage of NSCLC at incident diagnosis, age, sex, geographical location, residency (rural versus urban), and date of death, among others. The RPDB contains demographic information and vital statistics on all residents of Ontario who are eligible for universal healthcare coverage in the province. The CIHI-DAD holds data on diagnoses and procedures for all in- and outpatient hospital admissions. The ODB database contains data on all prescription medications dispensed to persons eligible for publicly-funded

drug coverage, including those aged ≥65 years, living in homes for special care and long-term care homes, receiving professional services through the home or community care service programs, receiving social assistance, and receiving benefits through the Trillium Drug Program, a scheme which provides assistance for people with high prescription drug costs relative to their net household income. The ODB does not capture information covered by private insurance or compassionate use programs from manufacturers. The ALR system contains information on systemic and radiation therapy services and outpatient oncology clinic visits provided to persons diagnosed with cancer. The NDFP database contains information on indication for use of all publicly funded intravenous drug therapies administered in -hospital and -cancer clinics in Ontario. The NDFP is a publicly funded drug program in Ontario that covers the costs of many novel and expensive intravenous cancer therapies.

5.3.4. Covariates

We identified several sociodemographic and clinical factors that may influence treatment selection and outcomes (overall survival [OS] and costs) through the literature and inputs derived from consultation with an expert (Bergqvist et al., 2020; Booth et al., 2010; Charlson et al., 1987; Deyo et al., 1992; Girard, 2019; Kim et al., 2019; Lin et al., 2017; Schrijvers et al., 1997). These factors included year of diagnosis, age, sex, residency, neighborhood income quintile, geographical residency within the province (i.e., North, West, Toronto, Central, East), clinical stage, histology, CCI, and sites of metastasis (e.g., bone, brain, liver, lung).

Neighborhood household income was determined through linkage of postal codes to Canadian census data and was stratified into three tertiles, with the first and last tertiles representing neighborhoods with the lowest and highest income status, respectively. CCI was determined from hospitalization data using a two-year ‘look-back’ window and the scores were retrieved

from the most recent hospitalization record for each person. We followed Stavem et al.'s approach and considered missing comorbidities to be absent (Stavem et al., 2017). At the time of data collection, publicly funded healthcare services in Ontario were administered on a regional basis by 14 LHINs, each with its own distinct geographical territory. Recently, these LHINS were integrated into five regions consisting of North, West, Toronto Central, East, and South regions. We identified geographical residency based on these regions.

5.3.5. Outcomes

We conducted our cost-effectiveness analyses using life-year (LY) gained and quality-adjusted life-year (QALY) gained as our measures of effectiveness. LY was measured as OS using the Kaplan-Meier method to estimate the mean OS. The OS was calculated from the date of diagnosis of NSCLC to death (for any reason) or the last day of follow-up (censored). QALY was calculated as the product of the utility score and the mean OS. Due to a lack of available data on progression, a single utility value of 0.75 was used to estimate the QALYs (Jiang et al., 2019; Labbe et al., 2017). The analysis was conducted over a 68-month study period.

5.3.6. Costs

The present study only considered direct healthcare costs in accordance with the payer's perspective. Individual-level healthcare costs were computed using a macro-based costing methodology 'GETCOST', which is available at ICES (Wodchis, Bushmeneva, Nikitovic, & McKillop, 2013). The healthcare services that we costed in this study included in-patient hospitalization, out-patient clinic visits, same-day surgeries, emergency department (ED) visits, cancer clinic visits, prescription drugs, rehabilitation services, complex continuing care (CCC), long-term care (LTC), home care (HC), physician services, laboratory, mental health (MH) admissions, assistive devices, and NDFP.

Cost estimates for same-day surgeries and ED visits were obtained from the National Ambulatory Care Reporting System (NACRS) database. Cost estimates for hospitalization, same-day surgeries, and ED visits were estimated using the Resource Intensity Weight (RIW) methodology developed by CIHI (Jacobs, 2009). Costs associated with physician visits and laboratory tests were estimated from the physicians claims history in the Ontario Health Insurance Plan (OHIP) claims database. Costs associated with HC, LTC, and CCC were estimated from the HC, Continuing Care Reporting System (CCRS), and ODB databases. Costs of prescription drugs were obtained from the ODB database, while costs of NDFP drugs were measured per actual dose and estimated from the NDFP database. Costs associated with MH admissions were obtained from the Ontario Mental Health Reporting System (OMHRS).
All costs were adjusted for inflation to 2020 Canadian dollars using the Statistics Canada Consumer Price Index for health care and personal items for Ontario (Statistics Canada). Effectiveness and cost data were discounted at an annual rate of 1.5% (CADTH, 2017).

5.3.7. Statistical Analysis

A net benefits regression (NBR) framework was used to assess the comparative cost-effectiveness of afatinib, erlotinib, and gefitinib (Hoch & Dewa, 2008). We estimated the net benefit value for the *i*th person using the following formula: $NB = \lambda E_i - C_i$, where λ represented the pre-determined willingness-to-pay (WTP) threshold value, E_i represented the observed effect and C_i represented costs, for the *i*th person. Various ranges of λ values were explored in our analyses, ranging from $0 to $200,000 (Raymaykers et al., 2020). The general rule associated with NBR frameworks is to assume new interventions are cost-effective if INB >0 at a specified threshold λ.

NBR involved fitting a linear regression model adjusting for relevant covariates to the outcome (see Covariates above). Three separate regression models were constructed for afatinib versus gefitinib, afatinib versus erlotinib, and gefitinib versus erlotinib. We adjusted for propensity scores to minimize bias for non-random allocation of samples to EGFR-TKI treatment; propensity scores were included in the linear regression models to calculate INBs to generate ICERs and uncertainty measures. A propensity score is each participant's probability of being assigned to the exposed/treatment group given a set of observed individual covariates (Austin, 2011). We calculated the propensity scores using logistic regression models with EGFR-TKI treatment as the dependent variable and the covariates described above as independent variables.

Censored observations were taken into account by using inverse probability of censoring weights (IPCW). Logistic regression was used to calculate the probability of being censored for each individual based on treatment and observed individual covariates. Individuals were weighted by the inverse of their predicted probability of not being censored. All independent variables included in the model were evaluated for multicollinearity prior to inclusion.

In its simplest form, NBR involves fitting a linear regression model with an equation:

$$NB_i = \beta_0 + \beta_1 TX_i + \varepsilon_i$$

Where NB_i is the person-level NB; β_0 is an intercept term; TX_i is the treatment indicator (i.e., $TX_i = 1$ for new treatment and 0 for usual care) and ε_i is the stochastic error term. The dependent variable NB_i is modelled as a function of relevant covariates and the error term. The regression coefficient β_1 provides the estimate of the incremental net benefit (INB) of new intervention versus the usual care accounting for λ.

Our final NBR model was as follows:

$$NB_i = \beta_0 + \beta_1(\text{EGFR-TKI})_i + \beta_2(\text{age})_i + \beta_3(\text{sex})_i + \beta_4(\text{year of diagnosis})_i + \beta_5(\text{rural versus urban})_i + \beta_6(\text{neighborhood income})_i + \beta_7(\text{geographical residency})_i + \beta_8(\text{clinical stage})_i + \beta_9(\text{comorbidities})_i + \beta_{10}(\text{liver metastasis})_i + \beta_{11}(\text{bone metastasis})_i + \beta_{12}(\text{brain metastasis})_i + \beta_{13}(\text{lung metastasis})_i + \beta_{14}(\text{propensity score})_i + \varepsilon_i$$

IPCW were applied to the model to account for differential censoring. Statistical significance was set at α=0.05. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and STATA version 12.0 (Stata Corporation, College Station, TX).

5.3.8. Sensitivity Analysis

To characterize the uncertainties associated with INB estimates, three sensitivity analyses were conducted. First, a one-way deterministic sensitivity analysis was conducted to examine the impact of varying utility scores on the ICER by using the lower and upper bounds of the health state utilities (±0.04). Second, the INB and its 95% CI were plotted against various ranges of λ values. Third, we used non-parametric bootstrapping to draw 1,000 samples of INB estimates and constructed cost-effectiveness acceptability curves (CEACs). A CEAC displays the probability that an intervention is cost-effective compared to its alternative under ranges of λ values.

5.4. Results

A total of 547 patients met the eligibility criteria and were included in the study (Table 8). Of these, 110 (20.1%) received afatinib, while 129 (23.6%) and 308 (56.3%) patients received erlotinib and gefitinib, respectively. Over half of the study sample (51.9%) were aged 70 to 79

years and 39.3% were males. Almost all patients (98.7%) had non-squamous histology and had stage IV NSCLC (91.4%) at time of diagnosis.

Table 8 Baseline Characteristics of the Study Population

	Afatinib	Erlotinib	Gefitinib	Total
	n = 110 (%)	n = 129 (%)	n = 308 (%)	n = 547 (%)
Year of Diagnosis				
2014-2016	52 (47.3%)	125 (96.9%)	205 (66.6%)	382 (69.8%)
2017-2019	58 (52.7%)	4 (3.1%)	103 (33.4%)	165 (30.2%)
Age, years				
18-59	36 (32.7%)	25 (19.4%)	62 (20.1%)	123 (22.5%)
60-69	15 (13.6%)	24 (18.6%)	32 (10.4%)	71 (13.0%)
70-79	55 (50.0%)	70 (54.3%)	159 (51.6%)	284 (51.9%)
80+	4 (3.7%)	10 (7.7%)	55 (17.9%)	69 (12.6%)
Sex				
Male	44 (40.0%)	71 (55.0%)	100 (32.5%)	215 (39.3%)
Female	66 (60.0%)	58 (45.0%)	208 (67.5%)	332 (60.7%)
Rurality				
Rural	15 (13.6%)	17 (13.2%)	28 (9.1%)	60 (11.0%)
Urban	95 (86.4%)	112 (86.8%)	280 (90.9%)	487 (89.0%)
Neighborhood Income Quintile				
1 (poorest)	57 (51.8%)	63 (48.8%)	127 (41.2%)	247 (45.2%)
2	16 (14.6%)	25 (19.4%)	55 (17.9%)	96 (17.5%)
3 (wealthiest)	37 (33.6%)	41 (31.8%)	126 (40.9%)	204 (37.3%)
Geographical Residency				
North	11 (10.3%)	9 (7.0%)	10 (3.3%)	30 (5.5%)
West	27 (25.2%)	38 (29.5%)	62 (20.3%)	127 (23.5%)
Toronto	9 (8.4%)	8 (6.2%)	42 (13.8%)	59 (10.9%)
Central	34 (31.8%)	30 (23.2%)	126 (41.3%)	190 (35.1%)
East	26 (24.3%)	44 (34.1%)	65 (21.3%)	135 (25.0%)
Clinical Stage				
IIIB	11 (10.0%)	13 (10.1%)	23 (7.5%)	47 (8.6%)
IV	99 (90.0%)	116 (89.9%)	285 (92.5%)	500 (91.4%)
Histology				
Non-squamous	109 (99.1%)	127 (98.5%)	304 (98.7%)	540 (98.7%)
Squamous Cell	0	0	0	0
NOS	1 (0.9%)	2 (1.5%)	4 (1.3%)	7 (1.3%)
CCI				
No	107 (97.3%)	119 (92.2%)	295 (95.8%)	521 (95.2%)
Yes	3 (2.7%)	10 (7.8%)	13 (4.2%)	26 (4.8%)
Site of Metastasis				
Liver	16 (14.6%)	25 (19.4%)	31 (10.1%)	72 (13.2%)
Bone	40 (36.4%)	38 (29.5%)	121 (39.3%)	199 (36.4%)
Brain	26 (23.6%)	18 (14.0%)	69 (22.4%)	113 (20.7%)
Lung	19 (17.3%)	30 (23.3%)	68 (22.1%)	117 (1.4%)

CCI: Charlson Comorbidity Index

5.4.1. Outcomes

Effectiveness and incurred costs were stratified according to each treatment and are summarized in Table 9. Highest survival was observed among persons who received afatinib as first-line treatment (mean LY: 2.67, standard error [SE]: 0.16), followed by persons who received gefitinib (mean LY: 2.23, SE: 0.10) and erlotinib (mean LY: 1.68, SE: 0.10). Furthermore, afatinib was associated with the lowest costs (mean costs: $130,717), followed by gefitinib (mean costs: $137,037) (Table 10).

Table 9 Effectiveness and Cost Estimates

Treatment Strategies (% Censored)	Median LY (95% CI)	Mean LY (SE)	Mean QALY (SE)	Mean Total Costs (Range)
Afatinib (48%)	2.59 (1.95-3.50)	2.67 (0.16)	2.00 (0.12)	130,716.68 (8,177.45-400,348.60) SD: 78812.38
Erlotinib (7%)	1.32 (1.24-1.54)	1.68 (0.10)	1.26 (0.08)	169,243.46 (47,033.15-450,526.45) SD: 78411.16
Gefitinib (31%)	1.79 (1.55-1.96)	2.23 (0.10)	1.67 (0.08)	137,036.99 (291.10-467,488.15) SD: 76477.33

CI: Confidence Interval; LY: Life Year; QALY: Quality-Adjusted Life Year; SD; Standard Deviation; SE: Standard Error

Table 10 Breakdown of Total Costs

Cost Source	Overall Mean Cost (Range)	Afatinib Mean Cost (Range)	Erlotinib Mean Cost (Range)	Gefitinib Mean Cost (Range)
Total Costs	143361.30 (291.10-467488.15) SD: 78632.11	130716.68 (8177.45-400348.60) SD: 78812.38	169243.46 (47033.15-450526.45) SD: 78411.16	137036.99 (291.10-467488.15) SD: 76477.33
In-patient hospitalization	25090.52 (0-178152.18) SD: 26333.77	21743.27 (0-119464.78) SD: 25099.50	29155.44 (0-120460.05) SD: 24178.75	24583.44 (0-178152.18) SD: 27471.71
Outpatient clinic visits	7912.29 (0-42995.68) SD: 6216.77	6657.11 (0-27338.80) SD: 5403.77	8176.77 (0-35198.50) SD: 5569.60	8249.79 (0-42995.68) SD: 6687.79
Same-day surgery	2471.37 (0-19208.50)	2290.01 (0-19208.50)	2672.62 (0-18792.35)	2451.86 (0-15671.23)

Cost Source	Overall Mean Cost (Range)	Afatinib Mean Cost (Range)	Erlotinib Mean Cost (Range)	Gefitinib Mean Cost (Range)
	SD: 2667.61	SD: 2794.73	SD: 3044.31	SD: 2447.38
Emergency department Visits	2813.22 (0-30524.50) SD: 2595.08	2342.25 (0-14563.20) SD: 2277.13	3570.00 (0-30524.50) SD: 3427.56	2664.46 (0-14562.18) SD: 2212.59
Cancer clinic visits	22336.17 (0-198436.93) SD: 26457.13	22192.61 (0-140651.53) SD: 28527.53	36813.12 (0-198436.93) SD: 29721.66	16324.04 (0-132446.40) SD: 21524.85
ODB drugs	33478.92 (0-182181.45) SD: 29449.72	35573.95 (0-146303.38) SD: 30490.40	21822.08 (92.25-142963.93) SD: 22376.94	37612.94 (0-182181.45) SD: 30459.91
Rehabilitation	1143.97 (0-48648.55) SD: 5056.56	1112.69 (0-33125.95) SD: 4950.02	1606.33 (0-48648.55) SD: 6248.40	961.50 (0-42104.95) SD: 4513.60
Complex continuing care	2577.28 (0-118475.65) SD: 10415.11	1933.45 (0-78289.50) SD: 9819.49	2323.09 (0-69718.45) SD: 8455.00	2913.69 (0-118475.65) SD: 11339.86
Long-term care	100.04 (0-17135.95) SD: 1122.05	0	250.89 (0-17135.95) SD: 2010.63	72.59 (0-7942.73) SD: 734.64
Home care	7664.91 (0-66026.40) SD: 10785.52	5514.78 (0-52194.03) SD: 8251.22	10949.54 (0-66026.40) SD: 12773.20	7057.10 (0-61893.60) SD: 10398.56
Physician services (OHIP)	27714.59 (196.80-101735.35) SD: 13880.35	26461.58 (2171.98-68529.45) SD: 13211.40	29256.85 (9860.50-82756.45) SD: 13690.04	27516.14 (196.80-101735.35) SD: 14175.32
Laboratory (OHIP)	1747.89 (0-15386.28) SD: 1505.58	1602.08 (0-6515.93) SD: 1215.32	1651.89 (0-15386.28) SD: 1759.86	1840.17 (0-9895.35) SD: 1481.80
Mental health admissions	50.02 (0-9817.45) SD: 557.75	54.29 (0-4845.18) SD: 473.33	0	69.44 (0-9817.45) SD: 687.23
Assistive devices	27.05 (0-3113.95) SD: 182.16	12.42 (0-817.95) SD: 93.44	48.45 (0-3113.95) SD: 307.01	23.32 (0-817.95) SD: 127.82
NDFP drugs	6181.56 (0-114996.80) SD: 14333.66	2166.97 (0-72629.45) SD: 8734.07	18454.36 (0-114996.80) SD: 20144.24	2475.12 (0-87023.53) SD: 9288.59

SD: Standard Deviation; NDFP: New Drug Funding Program; ODB: Ontario Drug Benefit; OHIP: Ontario Health Insurance Plan

5.4.2. Net benefit regression

Incremental effectiveness (LY and QALY) and costs are summarized in Table 11. In the adjusted model, erlotinib was dominated by both afatinib and gefitinib, indicating erlotinib as the least cost-effective option among the three treatments. Compared to gefitinib, afatinib demonstrated higher effectiveness (incremental LY: 0.28, incremental QALY: 0.21) with higher incremental costs ($9,745). The ICER estimate for afatinib compared to gefitinib was $34,879 per LY gained or $46,506 per QALY gained.

Table 11 Adjusted Incremental Effectiveness, Incremental Costs, and Incremental Cost-Effectiveness Ratios

Treatment Strategies	Adjusted Incremental Effect (LY)	Adjusted Incremental Effect (QALY)	Adjusted Incremental Cost ($)	Adjusted ICER ($/LY gained)	Adjusted ICER ($/QALY gained)
Afatinib vs. Erlotinib	0.70	0.53	$-1,549	Erlotinib dominated	Erlotinib dominated
Afatinib vs. Gefitinib	0.28	0.21	$9,745	$34,879	$46,506
Gefitinib vs. Erlotinib	0.25	0.19	$-13,610	Erlotinib dominated	Erlotinib dominated

ICER: Incremental Cost-Effectiveness Ratio; LY: Life Year; QALY: Quality-Adjusted Life Year

The NB estimates for QALYs are summarized in Table 12 and Table 13 (Appendix G and Appendix H for LYs**)**. Afatinib was not cost-effective compared to gefitinib at WTP values ranging between $0 and $40,000/QALY gained. Beyond the WTP value of $46,506, afatinib was cost-effective over gefitinib. Year of diagnosis significantly increased NB at WTP values between $0 and 50,000/QALY gained. Metastasis to bone and brain significantly reduced NB at WTP values between $0-$50,000, and $0-$100,000/QALY gained, respectively. Age group significantly reduced NB at WTP values between $50,000 and $100,000/QALY gained, while female sex significantly increased NB at WTP values between $50,000 and $100,000/QALY gained. (Table 12).

Table 12 Net Benefit Estimates for Afatinib versus Gefitinib – QALY

Covariates NB (95% CI)	Net Benefits λ = 0		Net Benefits λ = 20000		Net Benefits λ = 50000		Net Benefits λ = 100000	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Constant Term	-125950 (-133886--118013)	-257218 (-336392--178043)	-101869 (-109121--94618)	-203726 (-276722--130730)	-65748 (-72811--58686)	-123489 (-193363--53614)	-5547 (-14480-3386)	10240 (-71678-92158)
Covariates								
Afatinib	5809 (-9662-21280)	-9745 (-22230-2739)	7620 (-6515-21756)	-5554 (-17065-5956)	10337 (-3431-24104)	732 (-10286-11750)	14865 (-2549-32278)	11210 (-1707-24127)
Year of diagnosis		64164 (48585-79744)*		52876 (38512-67240)*		35944 (22194-49693)*		7723 (-8396-23842)
Age Group		-4266 (-10656-2123)		-5441 (-11332-451)		-7202 (-12842--1563)***		-10138 (-16749--3527)**
Female Sex		7957 (-4948-20861)		10065 (-1833-21962)		13226 (1838-24615)***		18496 (5144-31847)**
Urban versus Rural		2907 (-16663-22477)		476 (-17566-18519)		-3169 (-20440-14102)		-9245 (-29493-11003)
Neighborhood Income		570 (-5475-6615)		-237 (-5810-5336)		-1447 (-6782-3887)		-3465 (-9719-2789)
Geographical Residency		-463 (-5059-4132)		-247 (-4484-3990)		78 (-3978-4133)		619 (-4136-5373)
Clinical Stage		17389 (-4684-39462)		13017 (-7334-33368)		6460 (-13021-25940)		-4470 (-27308-18368)
Comorbidity		13420 (-7261-34101)		8753 (-10314-27820)		1752 (-16500-20004)		-9916 (-31313-11482)
Bone Metastasis		-16232 (-31394--1071)***		-15467 (-29446--1489)***		-14319 (-27700--939)***		-12406 (-28093-3281)
Liver Metastasis		-11432 (-36192-13329)		-10796 (-33625-12032)		-9843 (-31695-12009)		-8255 (-33873-17364)
Lung Metastasis		2319 (-15924-20562)		3151 (-13668-19971)		4400 (-11700-20500)		6481 (-12394-25356)
Brain Metastasis		-21796 (-39069--4523)***		-21742 (-37667--5817)**		-21661 (-36905--6417)**		-21526 (-39397--3654)***
R-squared (adjusted)	0.0011	0.4274	0.0003	0.3979	0.0028	0.3053	0.0043	0.1079

***p<.05; **p<.01; *p<.001; CI: Confidence Interval

Table 13 Estimates of Incremental Net Benefit and Probability of Cost-Effectiveness of Afatinib, Erlotinib, and Gefitinib - QALY.

	Afatinib Versus Gefitinib			Afatinib Versus Erlotinib			Gefitinib Versus Erlotinib		
λ Threshold	INB Estimate (SE)	P-value	Probability of Cost-effectiveness	INB Estimate (SE)	P-value	Probability of Cost-effectiveness	INB Estimate (SE)	P-value	Probability of Cost-effectiveness
$0	-9745 (6350)	0.126	0.022	1549 (10948)	0.888	0.703	13610 (9458)	0.151	0.919
$10,000	-7650 (7579)	0.209	0.038	6811 (10328)	0.510	0.854	15511 (9070)	0.088	0.978
$20,000	-5554 (5855)	0.343	0.069	12074 (9792)	0.219	0.955	17411 (8750)	0.047	0.996
$30,000	-3459 (5700)	0.544	0.112	17337 (9353)	0.065	0.996	19312 (8506)	0.024	0.999
$40,000	-1363 (5616)	0.808	0.209	22600 (9025)	0.013	1.000	21213 (8345)	0.011	1.000
$50,000	732 (5604)	0.896	0.350	27862 (8822)	0.002	1.000	23113 (8271)	0.005	1.000
$60,000	2828 (5666)	0.618	0.518	33125 (8751)	<.001	1.000	25014 (8286)	0.003	1.000
$70,000	4923 (5799)	0.396	0.653	38388 (8817)	<.001	1.000	26915 (8391)	0.001	1.000
$80,000	7019 (5999)	0.243	0.752	43650 (9015)	<.001	1.000	28816 (8581)	0.001	1.000
$90,000	9114 (6258)	0.146	0.843	48913 (9338)	<.001	1.000	30716 (8852)	0.001	1.000
$100,000	11210 (6570)	0.089	0.893	54176 (9773)	<.001	1.000	32617 (9196)	<.001	1.000
$150,000	21687 (8695)	0.013	0.984	80489 (13148)	<.001	1.000	42121 (11745)	<.001	1.000
$200,000	32165 (11346)	0.005	0.992	106803 (17605)	<.001	1.000	51624 (15118)	0.001	1.000

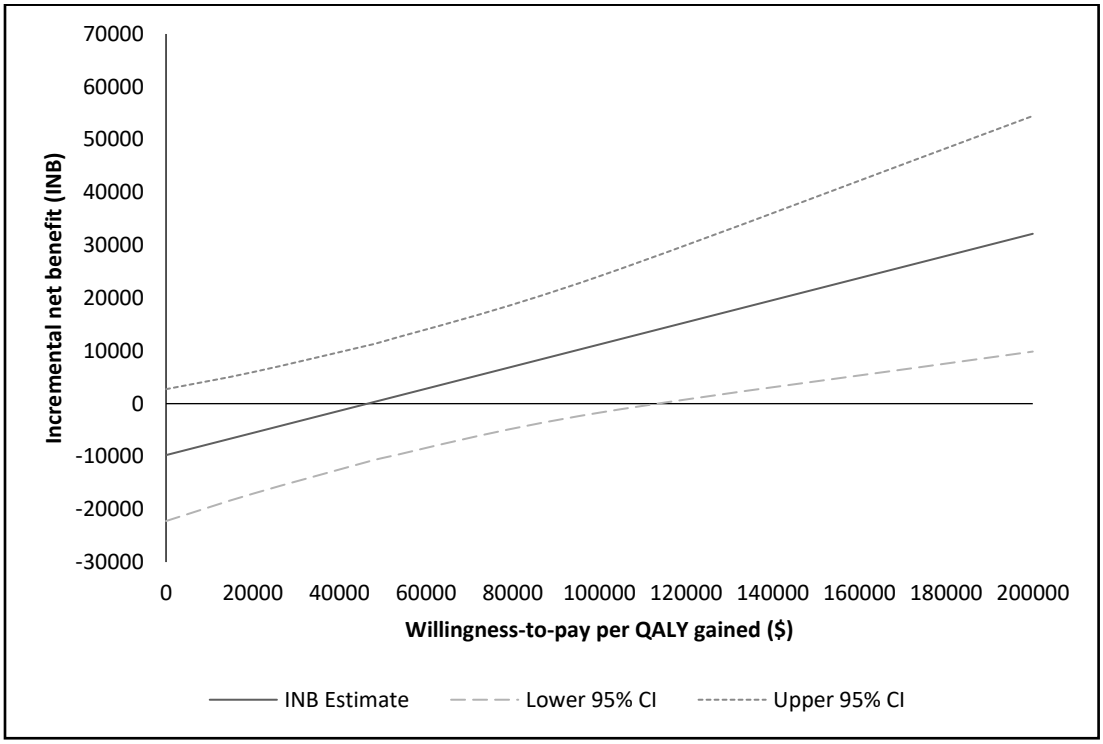
5.4.3. Sensitivity Analysis

Results from the one-way deterministic sensitivity analysis suggested the findings of the base-case analysis were robust. Erlotinib was dominated by both afatinib and gefitinib, while afatinib remained appear to be cost-effective over gefitinib under the WTP threshold of $50,000 per QALY gained, with ICERs of $49,126 and $44,151 per QALY gained for lower and upper bounds of health state utilities, respectively.

Figure 11 (Appendix I for LYs) depict INB estimates and its 95% CIs by range of WTP values. The ICER estimate can be visually seen on the graph where the INB estimate equals to zero on the x-axis. The 95%CI of the INB estimate suggest there is uncertainty of cost-effectiveness of afatinib at a WTP value of $46,506 (ICER) per QALY gained. However, at a WTP value of approximately $110,00 per QALY gained and beyond, afatinib is significantly cost-effective as indicated by the INB estimates and its confidence intervals >0.

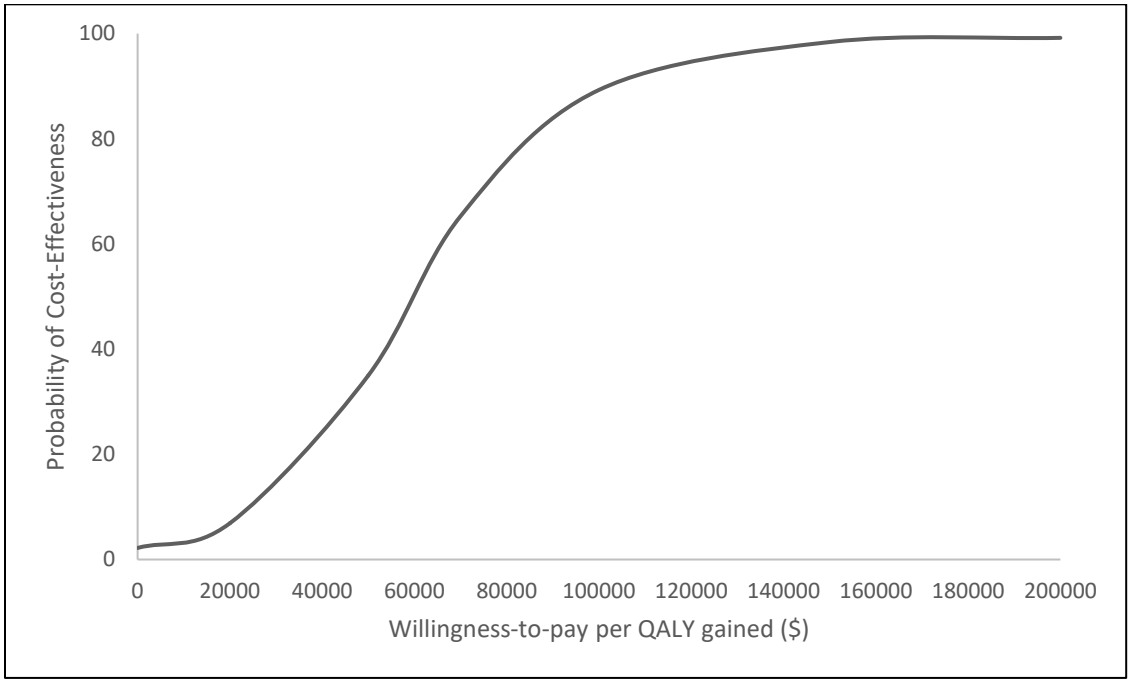
Figure 12 (Appendix J for LYs) depict the probability of cost-effectiveness of afatinib over gefitinib as a function of WTP threshold for additional QALY. The results showed that at the commonly cited WTP value of $50,000/QALY gained, afatinib had 35.0% probability of being cost-effective. At the WTP value of $100,000/QALY gained, afatinib had 89.3% probability of being cost-effective.

Figure 11 Incremental Net Benefit by Willingness-To-Pay for Afatinib versus Gefitinib - QALY



QALY: Quality-Adjusted Life Year

Figure 12 Cost Effectiveness Acceptability Curve for Afatinib versus Gefitinib - QALY



QALY: Quality-Adjusted Life Year

5.5. Discussion

The present study assessed the comparative cost-effectiveness of three first-line EGFR-TKIs for treatment of NSCLC. The results of our analysis suggest erlotinib as the least cost-effective option and afatinib as the most cost-effective treatment under the commonly cited $50,000/QALY gained WTP threshold. Though afatinib demonstrated higher effectiveness (incremental QALY: 0.21) compared to gefitinib, the additional benefits were associated with higher costs (incremental cost: $9,745), which resulted in an ICER estimate of $46,506 per QALY gained. This notion was also ascertained as shown in the CEAC where afatinib had 35.0% probability of being cost-effective under a commonly cited WTP threshold of $50,000/QALY gained.

Most cost-effectiveness analyses conducted for first-line EGFR-TKIs were assessed using information inferred from RCTs. Due to a lack of head-to-head data, previous studies measured effectiveness through indirect treatment comparisons from distinct RCTs. *Lee et al.* assessed the cost-effectiveness of erlotinib versus gefitinib and found an ICER estimate of $62,419 per QALY gained; however, the effectiveness was estimated through indirect comparison using OPTIMAL and IPASS trials (Lee et al., 2014). Similarly, *Ting et al.* calculated an ICER estimate of $61,809 per QALY gained for erlotinib versus gefitinib through indirect comparison (Ting et al., 2015), while *Chouaid et al.* calculated an ICER estimate of €45,211 per QALY gained for afatinib versus gefitinib using a head-to-head data from LUX-Lung 7 trial (Chouaid et al., 2017). Recently, *Yang et al.* directly compared the cost-effectiveness of three EGFR-TKIs and found afatinib was dominated by erlotinib, while erlotinib had an ICER estimate of $12,782 per QALY gained compared to gefitinib (Yang et al., 2020). *Arrieta et al*. found that erlotinib was dominated by afatinib and gefitinib, and suggested afatinib as the most cost-effective option with an ICER of $18,640 Mexican pesos/LY gained compared to gefitinib (Arrieta et al., 2020). However, both *Yang et al. and Arrieta et al*. used data sourced from a single institution and the findings may not be generalizable to broader populations (Arrieta et al., 2020; Yang et al., 2020). In contrast, our study directly assessed the cost-effectiveness of all three EGFR-TKIs by using population-based, linked administrative datasets, albeit limited to a single Canadian province, which captured all relevant data and complete follow-up for all patients.

Given the fact that approximately 15% of patients with non-squamous histology harbor *EGFR* mutation, we expected to identify a larger sample for our study. However, the relatively small sample size may be attributed to the initial challenges of implementation of biomarker testing in Ontario in the early 2010s, along with its associated logistical difficulties (e.g., delayed

turnaround times), which led chemotherapy to be used as the first-line treatment to avoid clinical deterioration (Cheema et al., 2017; Ellis et al., 2013). A previous study has suggested that approximately 1 in 4 patients do not undergo biomarker testing (Spicer, 2015).

A strength of adopting NBR to conduct a cost-effectiveness analysis is the capability of adjusting for important covariates to obtain more accurate estimates of INB and its corresponding ICERs. In our analysis, we found several covariates associated with NB ($p<0.05$), including year of diagnosis (λ from \$0-\$50,000), age group (λ from \$50,000-\$100,000), female sex (λ from \$50,000-\$100,000), bone metastasis (λ from \$0-\$50,000), and brain metastasis (λ from \$0-\$100,000). Contrary to previously published studies whereby estimates of effectiveness and treatment-related costs were inferred from multiple sources, our study was able to establish head-to-head comparisons of these measures, which emulates the routine clinical practice associated with management of NSCLC. In this sense, the findings of our study minimized some of the threats to external validity that arise in RCT-driven model-based analyses.

Our study had several limitations. First, while Ontario is the most populous and ethnically diverse province in Canada, the generalizability of our results to other populations is unclear. Second, the number of patients who received erlotinib between 2017-2019 was relatively small compared to patients who received afatinib and gefitinib. This could be explained by the fact that erlotinib is only publicly funded for second- and third-line settings in Ontario, though it has an indication for first-line treatment, as well. Another explanation may be that prescription of erlotinib gradually declined in clinical practice over the years. Third, the medication claims data indicate that a medication was dispensed, but we cannot determine whether the medication was actually used. Lastly, we useda mean HUS to estimate the QALYs for all EGFR-TKIs in our

analysis due to lack of data on progression. However, it is worth noting that several studies have reported comparable estimates of mean HUS across EGFR-TKIs where differences observed in mean HUS were very marginal (±0.01) (Jiang et al., 2019).

Though the NBR model can adjust for influential covariates to obtain more accurate INB estimates, our model could not adjust for factors that were not observed or captured in the databases. These factors may include treatment sequencing, growing familiarity with new agents among practitioners, regional/institutional preference, reimbursement, and influence of pharmaceutical companies, among others (Fleischman et al., 2016; Schumock et al., 2004), though the applicability of these factors to EGFR-TKIs is unknown. Furthermore, previous studies have demonstrated the importance of Eastern Cooperative Oncology Group Performance Status (ECOG-PS) and type of *EGFR* mutation status (e.g., Exon19DEL, L858R) as important factors in treatment selection and survival (Cha et al., 2015; Hung et al., 2018; Jackman et al., 2006; Pirker et al., 2012) However, a lack of data on ECOG-PS and *EGFR* mutation status prohibited us from carrying out further analyses involving these factors. We assumed that patients who received any of the three EGFR-TKI had positive *EGFR* mutation, regardless of the type. Although highly unlikely, we cannot rule out the possibility that TKIs may have been prescribed to EGFR wild-type patients. Lastly, since the ODB data do not capture information on private insurance claims and compassionate supplies, we were not able to assess prescribing differences stratified by payer type.

5.6. Conclusion

The results of the present study demonstrated that erlotinib was dominated by afatinib and gefitinib, while afatinib had an ICER estimate of $34,879 per LY gained or $46,506 per QALY gained compared to gefitinib. From our analysis, afatinib appears to be the most cost-effective

treatment among the three examined, if a threshold of $50,000/QALY gained was to be chosen. Additional studies using population-based, longitudinal data are required to accurately assess the cost-effectiveness of first-line EGFR-TKI.

Chapter 6: Discussion

6.1. Implications for Clinical Practice

Emerging research on treatment sequencing for *EGFR*-mutant NSCLC is promising, although it is not entirely clear which treatment sequence provides the best outcomes for each individual patient. In addition to treatment effectiveness and tolerability, several other factors are considered for treatment selection such as patient characteristics, patient preferences, and anticipated quality of life. Furthermore, given that all patients will inevitably experience disease progression during the use of EGFR-TKIs, subsequent therapy is an important consideration when choosing first-line treatment.

Osimertinib is now recommended as the preferred first-line option for *EGFR* mutation-positive NSCLC. The results of the FLAURA study demonstrated prolonged OS with the use of osimertinib compared to first-generation TKIs in the first-line setting: 38.6 months (95%CI: 34.5-41.8) vs. 31.8 months (95%CI: 26.6-36.0) (Ramalingam et al., 2020). However, the downside of the front-line use of osimertinib is the lack of subsequent treatment options in later lines of therapy; however, it is worth noting that approximately 30% of patients with EGFR-mutated NSCLC never go on to receive a second-line therapy (Ramalingam et al., 2020).

Alternative to upfront use of osimertinib, growing body of evidence suggest sequential afatinib followed by osimertinib as another treatment option in the first-line setting. A post hoc analysis of LUX-Lung 3, 6, and 7 studies demonstrated improved OS in patients who received osimertinib following afatinib therapy (3-year OS: 90%) (Sequist et al., 2017). Furthermore, results from the global, retrospective, real-world GioTag study, which investigated the use of afatinib followed by osimertinib showed a favorable rate of 2-year survival (80%), a median time

to treatment failure of 28.1 months, and OS rate of 45.7 months with sequential use (Hochmair et al., 2019). However, the findings of GioTag study should be interpreted with caution as potential immortal time bias may have been introduced as patients who died on afatinib or were unfit or unwilling to receive a second-line therapy were excluded from the study. Therefore, patients enrolled into the GioTag study may represent a healthier population and the estimates of health outcomes may be overestimated. A recent retrospective study among T790M mutation-positive patients who acquired resistance to first-generation TKIs (i.e., erlotinib and gefitinib) and afatinib during any line of therapy showed higher rates of ORR and prolonged disease control with the use of afatinib followed by osimertinib, versus the use of first-generation TKIs followed by osimertinib (Tamiya et al., 2018). The favorable outcomes suggest that the benefits of afatinib may extend beyond the first-line treatment. The findings of Chapter 4 and Chapter 5 of this dissertation are consistent with previous studies where higher efficacy/effectiveness was observed with the use of afatinib relative to first-generation TKIs.

Apart from EGFR-TKIs, immunotherapy and combination of EGFR-TKIs and immunotherapy as first-line treatment has garnered much attention lately. Pre-clinical studies have shown that EGF-stimulated *EGFR* activation leads to PD-L1 overexpression by tumor cells through the ERK1/2-c-jun pathway (Chen et al., 2015). This suggests that the combination of anti-PD-1/PD-L1 and EGFR-TKIs may have synergetic effects in NSCLC therapy. Although many trials have attempted to investigate this combination in pre-treated NSCLC cases with promising clinical activity, higher incidence of AEs, with most of them being grade 3/4, impeded the progress of these studies and even led to termination (Ahn et al., 2017; Yang et al., 2019). To date, combined PD-(L)1 inhibition and chemotherapy has shown clinical benefits in patients with *EGFR* wild-type NSCLC and has now become the standard of care; however, the role of PD-(L)1 inhibitors

in *EGFR*-mutant NSCLC remains incompletely defined. A phase II trial of pembrolizumab in PD-L1 positive *EGFR*-mutated NSCLC in the first-line setting showed lack of efficacy, which resulted in termination of enrollment (Lisberg et al., 2018). Furthermore, increased risk of pneumonitis and hepatitis was observed in the study when subsequent EGFR-TKIs were administered close to or with an ICI (Lisberg et al., 2018). Therefore, PD-(L)1 inhibitors as single agents or in combination with a platinum doublet should not be used in the first-line treatment of *EGFR*-mutated NSCLC, and PD-L1 expression levels should not be used to select first-line treatment for *EGFR*-mutated NSCLC.

Available data to date suggest that the efficacy/effectiveness of second- and third-generation EGFR-TKIs is superior to that of first-generation agents, despite a higher incidence of grade 3/4 AEs. Based on the findings of this dissertation and previous studies, first-line treatment with afatinib may represent an optimal sequencing strategy for the majority of patients with *EGFR* mutation-positive NSCLC from both clinical and cost-effectiveness perspective among the available first- and second-generation EGFR-TKIs.

6.2. Implications for Healthcare System

As described previously, each chapter of this dissertation has independently advanced decision-making around optimal treatment sequencing and resource allocation associated with treatments for NSCLC. Maintaining a sustainable healthcare system requires decision-makers to not only consider resource allocation decisions at the introduction of novel therapies, but also to periodically revise allocation decisions for previously reimbursed interventions. Despite the comprehensive review and assessment of new health technologies, the recommendations and decisions for reimbursements are often accompanied with many uncertainties. A major source of these uncertainties is largely the estimates of input parameters used in the models due to lack of

data. The most common way that parameter uncertainties are introduced into a model is by using data from sources that represent a different patient population or country, and assumptions in the absence of data. Longitudinal data continuously accumulated over the years allows us to reassess these uncertainties and generate more accurate evidence for reimbursement decisions. This dissertation demonstrated that with population-based, longitudinal, person-level administrative data, employment of a simple regression technique allows for the generation of real-world evidence of effectiveness, healthcare resource utilization, and costs for previously reimbursed therapies. To date, the present dissertation was the first of its kind to generate real-world evidence on the comparative clinical and cost-effectiveness of EGFR-TKIs in Canada. The findings of the studies presented in this dissertation contributes to the body of knowledge on comparative effectiveness of EGFR-TKIs and may assist healthcare decision-makers in improving resource allocation decisions.

6.3. Limitations and Future Research

The studies presented in this thesis has several limitations that are common to studies using claims and medical records databases. First, claims data are primarily collected for reimbursement purposes rather than research purposes. On a related matter, information on claims are subject to errors of omission and/or commission. Without access to patients' medical records for verifications, it is possible that some patients in the study sample may have been misclassified by their histological subtypes (SCLC versus NSCLC) or other measures of interest (e.g., clinical stage). Second, studies pertaining to Chapter 4 and Chapter 5 included patients drawn from the OCR, which comprise population only in Ontario; generalizability of results to the Canadian population as a whole or other countries may be limited. Third, prescription claims do not contain information on the indication(s) for which the medications are dispensed.

Moreover, pharmacy claims indicate that a medication was dispensed, but not whether or how it was used. Relatedly, healthcare claims will not include information on medications administered during hospitalizations, or of the dispensing and use of free samples. However, it is worth noting that the impact of this issue is likely minimal since EGFR-TKIs are dispensed mainly from specialty pharmacies on outpatient basis. Lastly, as with all real-world data studies, there may have been unmeasured confounding and missing data (e.g., *EGFR* mutation status, ECOG-PS), which may have had an impact on the estimates of study outcomes.

Several areas for future research have been identified through the research conducted for this dissertation. First, while pre-clinical and clinical studies have shown promising results and feasibility of the use of combination regimens consisting of EGFR-TKIs and immunotherapies as first-line treatment for *EGFR* mutation-positive NSCLC, there were no clear signals that this may be an effective strategy. While Chapter 3 of this thesis demonstrated effectiveness consistent with what was observed in the trials for nivolumab, the results are not specific to *EGFR* mutation-positive NSCLC. Further understanding of differences in the tumor microenvironment between *EGFR* mutant and *EGFR* wild-type NSCLC will be necessary for proper drug development in this patient population. A recent study by *Yang et al*. reports gefitinib plus immunotherapy (i.e., pembrolizumab) is not tolerable and this is clear (Yang et al., 2019). However, findings supporting the notion that erlotinib plus pembrolizumab are safe are somewhat premature (Yang et al, 2019). Several phase I/II trials investigating the combination of PD-(L)1 inhibitors and EGFR-TKIs failed to show additive activity compared to EGFR-TKI monotherapy (Ahn et al., 2016; Creelan et al., 2019; Gettinger et al., 2018; Rudin et al., 2018; Yang et al., 2019). Moreover, clear safety signals emerged, which led to early discontinuation of enrollment and/or trials investigating the combination of ICIs and EGFR-TKIs (Ahn et al., 2016;

Yang et al., 2019). However, the clinical benefits of combination ICI and chemotherapy in *EGFR*-mutant NSCLC remain investigative; the IMpower150 trial demonstrated improved PFS and OS among patients who received carboplatin/paclitaxel in combination with atezolizumab and bevacizumab compared with carboplatin/paclitaxel with bevacizumab or atezolizumab (Socinski et al., 2018). However, the IMpower130 trial failed to show a survival benefit in the subset of population with *EGFR*/*ALK* alterations, despite demonstrating PFS and OS benefits in the wild-type population (West et al., 2019). Larger, prospective studies should be conducted to verify these findings before a definitive role of ICI and chemotherapy can be pronounced for patients with *EGFR*-mutant lung cancer. Note, there are currently two large phase III trials ongoing: 1) KEYNOTE-789 comparing platinum-doublet chemotherapy with/without pembrolizumab in patients with TKI-resistant *EGFR*-mutant NSCLC, and 2) CheckMate 722 comparing platinum-doublet chemotherapy with/without nivolumab in patients with metastatic *EGFR*-mutant NSCLC after disease progression on first- or second-line EGFR inhibition.

The findings of this thesis support afatinib as the optimal first-line treatment for *EGFR*-mutant NSCLC. However, it is worth noting that osimertinib, which is now the preferred first-line treatment, was not considered in the studies (Chapter 4 and Chapter 5) due to lack of data. While several studies have demonstrated superior efficacy of front-line use of osimertinib (Cheng et al., 2021; Ramalingam et al., 2020; Soria et al., 2018), lack of subsequent treatment options, along with high acquisition costs connote that osimertinib may not be the most cost-effective option in the first line setting (Aguiar et al., 2018; Wu et al., 2018). A head-to-head trial of afatinib versus osimertinib, or large, population-based, longitudinal studies of outcomes and costs associated with consecutive sequencing of EGFR-TKIs is needed before any conclusions can be reached.

Strategies for the management of NSCLC are evolving faster than ever before with new generations of treatments and novel therapies emerging rapidly. While new technologies improve health outcomes, they come with their own set of concerns, including high costs, uncertainties in effectiveness, and complicated treatment sequences. To inform decision-making in this area, this dissertation provides up-to-date evidence on the comparative- and cost-effectiveness of EGFR-TKIs and immunotherapies.

The goal of this dissertation was to generate high-quality evidence that would ultimately lead to more informed decision-making for the management of NSCLC. The evidence generated by this dissertation work provides insight on the treatment patterns and use of EGFR-TKIs in Ontario at the population-level. Furthermore, the studies in this dissertation provides important parameter estimates that may be used in future studies assessing the cost-effectiveness of treatments that can be used to revise reimbursement decisions (e.g., upon maturity of data on osimertinib or introduction of subsequent generation of EGFR-TKIs).

Chapter 7: Summary of Key Points

7.1. What We Knew

- While EGFR-TKIs demonstrated superior efficacy over standard chemotherapy for the treatment of *EGFR* mutation-positive NSCLC in the first line setting, the comparative effectiveness of first- and second-generation EGFR-TKIs in the real-world settings remained unclear.

- Available EGFR-TKIs were assumed to be used interchangeably in clinical practice, though the degree to which patient characteristics affected prescribing decisions and overall survival remained largely unknown.

- Studies published to date have shown mixed implications in comparative cost-effectiveness of EGFR-TKIs.

- While immunotherapies have shown superior efficacy over standard chemotherapy in the second line setting among *EGFR* wild type lung cancer patients, the effectiveness in clinical practice remained unknown.

7.2. What the Dissertation Adds to the Literature

- Identified patient demographic (e.g., age, sex, geographic residency) and clinical (e.g., sites of metastasis, comorbidities) factors influencing treatment selection and overall survival associated with first-line EGFR-TKIs.

- Estimated comparative cost-effectiveness of afatinib, erlotinib, and gefitinib. In Ontario, afatinib was shown to be more cost-effective over erlotinib and gefitinib, while erlotinib was the least cost-effective option in the first line setting.

- The effectiveness of nivolumab was consistent with what was reported in the clinical trials, though the application to EGFR-mutant NSCLC remains unknown.

7.3. What We Need to Do Next

- Conduct trials and RWE studies to investigate the comparative clinical/cost-effectiveness between osimertinib versus afatinib for the treatment of *EGFR* mutation-positive NSCLC in the first line setting.

- Perform similar analyses using real-world data (e.g., registries, claims data, electronic health records) from other countries to compare and support the findings of the present dissertation.

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APPENDICES

Appendix A. Search Strategy

PubMed

(lung neoplasm[MeSH:noexp] OR Carcinoma, Non-Small-Cell Lung[MeSH] OR NSCLC*[tiab] OR lung adenocarcinom*[tiab] OR lung ca*[tiab]) AND (antibodies, monoclonal[MeSH: noexp] OR pembrolizumab[tiab] OR pembrolizumab[Supplementary Concept] OR nivolumab[tiab] OR nivolumab[MeSH] OR atezolizumab[tiab] OR atezolizumab[Supplementary Concept] OR immune checkpoint[tiab] OR PD-1[tiab] OR PD-L1[tiab]) AND (real world[tiab] OR real life[tiab] OR cohort studies[MeSH] OR cohort stud*[tiab] OR cohort analysis[tiab] OR "clinical experience"[tiab] OR "clinical practice"[tiab] OR retrospective stud*[tiab] OR retrospective analysis[tiab] OR prospective stud*[tiab] OR prospective analysis[tiab] OR follow-up stud*[tiab] OR longitudinal[tiab])

Web of Science

#	Searches
#1	(TS=("lung cancer*" OR "NSCLC" OR "lung adenocarcinoma" OR "lung carcinoma" OR "lung neoplasm")) *AND* **LANGUAGE**: (English) *AND* **DOCUMENT TYPES:** (Article) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2015-2019
#2	(TS=("pembrolizumab" OR "nivolumab" OR "atezolizumab" OR "immune checkpoint" OR "PD-1" OR "PD-L1")) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2015-2019
#3	(TS=("real world" OR "real life" OR "cohort" OR "retrospective" OR "prospective" OR "clinical practice" OR "clinical experience" OR "follow-up" OR "longitudinal")) *AND* **LANGUAGE:** (English) *AND* **DOCUMENT TYPES:** (Article)

#	Searches
	Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2015-2019
#4	#3 AND #2 AND #1 Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan=2015-2019

EMBASE

#	Searches
#1	exp non small cell lung cancer
#2	non small cell lung carcinoma.ab,ti.
#3	non small cell lung cancer.ab,ti.
#4	NSCLC.ab,ti.
#5	lung adenocarcinoma.ab,ti.
#6	(lung and (neoplasm$ or cancer$ or carcinom$)).ab,ti.
#7	1 or 2 or 3 or 4 or 5 or 6
#8	pembrolizumab.ab,ti.
#9	nivolumab.ab,ti.
#10	atezolizumab.ab,ti.
#11	exp cancer immunotherapy/
#12	pd-1.ab,ti.
#13	pd-l1.ab,ti.
#14	8 or 9 or 10 or 11 or 12 or 13
#15	7 and 14

#	Searches
#16	real world.ab,ti.
#17	real life.ab,ti.
#18	exp cohort analysis/
#19	cohort stud*.ab,ti.
#20	retrospective stud*.ab,ti.
#21	prospective stud*.ab,ti.
#22	follow up stud*.ab,ti.
#23	longitudinal*.ab,ti.
#24	clinical practice.ab,ti.
#25	clinical experience.ab,ti.
#26	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
#27	15 and 26
#28	27 not conference abstract.pt.
#29	limit 28 to English language

Appendix B. Quality assessment of included studies with modified Newcastle-Ottawa Scale

Case-Series							
Author	**Selection**			**Outcome**			**Score (Out of 6)**
	Representativeness of the Exposed Cohort (Maximum ★)	**Ascertainment of Exposure (Maximum ★)**	**Outcome Not Present at Start (Maximum ★)**	**Assessment of Outcome (Maximum ★)**	**Adequate Follow-up Length (Maximum ★)**	**Adequate Follow-up of Cohorts (Maximum ★)**	
Areses Manrique et al.	★	★	★	★			**4**
Bagley et al.	★	★	★	★			4
Brustugun, Sprauten & Helland	★	★	★	★	★		5
Costantini et al.	★	★	★	★	★	★	6
Crino et al.	★	★	★	★	★	★	6
Diem et al.	★	★	★	★			4
Dudnik et al.	★	★	★	★	★	★	6
Dumenil et al.	★	★	★	★			4
Facchinetti et al.	★	★	★	★	★		5
Fiorica et al.	★	★	★	★	★	★	6
Fujimoto et al.	★	★	★	★			4
Fukui et al.	★	★	★	★	★		5
Garde-Noguera et al.	★	★	★	★			4
Garassino et al.	★	★	★	★	★		5
Grossi et al.	★	★	★	★	★		5
Haratani et al.	★	★	★	★	★		5
Juergens et al.	★	★	★	★	★		5
Kataoka et al.	★	★	★	★			4
Kiriu et al.	★	★	★	★			4
Kobayashi et al.	★	★	★	★			4
Lesueur et al.	★	★	★	★	★		5
Merino Almazan et al.	★	★	★	★			4
Montana et al.	★	★	★	★			4
Sabatier et al.	★	★	★	★	★	★	6
Sato et al.	★	★	★	★			4
Schmid et al.	★	★	★	★	★		5
Schouten et al.	★	★	★	★			4

Case-Series							
Author	**Selection**			**Outcome**			**Score (Out of 6)**
	Representativeness of the Exposed Cohort (Maximum ★)	**Ascertainment of Exposure (Maximum ★)**	**Outcome Not Present at Start (Maximum ★)**	**Assessment of Outcome (Maximum ★)**	**Adequate Follow-up Length (Maximum ★)**	**Adequate Follow-up of Cohorts (Maximum ★)**	
Sekine et al.	★	★	★	★			4
Shamai & Merimsky	★	★	★	★	★		5
Shiroyama et al.	★	★	★	★	★		5
Takeda et al.	★	★	★	★			4
Tiu et al.	★	★	★	★			4
Tournoy et al.	★	★	★	★	★		5

Cohort									
Author	**Selection**				**Comparability**	**Outcome**			**Score (Out of 9)**
	Representativeness of the Exposed Cohort (Maximum ★)	**Selection of Non-exposed Cohort (Maximum ★)**	**Ascertainment of Exposure (Maximum ★)**	**Outcome Not Present at Start (Maximum ★)**	**Comparability (Maximum ★★)**	**Assessment of Outcome (Maximum ★)**	**Adequate Follow-up Length (Maximum ★)**	**Adequate Follow-up of Cohorts (Maximum ★)**	
Calpe-Armero et al.	★	★	★	★	★	★			6
Ksienski et al.	★	★	★	★	★	★	★		7
Yoo et al.	★	★	★	★	★	★			6

Appendix C. Summary of studies investigating the association between independent factors and overall survival associated with nivolumab

Author	Sample Size	Intervention	Stratified Median OS Months (95%CI)	HR (95%CI)	P-value
Age					
Areses Manrique et al.	188	Nivolumab 3mg/kg per 2 weeks	Age <70: 12.8 (NR) Age ≥70: 14.85 (NR)	NR	0.32
Bagley et al.	175	Nivolumab 3mg/kg per 2 weeks	NR	Age (<75 vs. ≥75): 1.1 (0.7-1.8)	NR
Diem et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	Age (per year): 1.01 (0.96-1.06)	0.841
Dudnik et al.	260	Nivolumab 3mg/kg per 2 weeks	Age <75: 6.3 (5.1-8.6) Age ≥75: 4.7 (3.3-8.6)	1.02* (0.99-1.04)	0.06
Dumenil et al.	67	Nivolumab 3mg/kg per 2 weeks	NR	Age (<70 vs. ≥70): 0.22 (0.81-2.59)	0.215
Facchinetti et al.	54	Nivolumab 3mg/kg per 2 weeks	Age <70: 7.0 (NR) Age ≥70: 6.6 (2.1-11.1)	NR	0.699
Fukui et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	Age (<75 vs. ≥75): 0.34 (0.08-1.45)	0.15
Garde-Noguera et al.	175	Nivolumab 3mg/kg per 2 weeks	Age <70: 7.1 (NR) Age ≥70: 5.8 (NR)	NR	0.794
Grossi et al.	371	Nivolumab 3mg/kg per 2 weeks	Age <65: 8.6 (5.2-11.9) Age 65-<75: 8.0 (5.6-10.4) Age ≥75: 5.8 (3.5-8.1)	Age (≥75 vs. 65-<75): 1.15 (0.82-1.61)	0.42
Juergens et al.	472	Nivolumab 3 mg/kg per 2 weeks	Age <65: 11.50 (9.04-14.10) Age 65-75: 12.60 (10.97-17.70) Age >75: 12.10 (6.60-N/A)	Age (65-75 vs. <65): 0.88 (0.68-1.15) Age (>75 vs. <65): 0.89* (0.60-1.33)	0.35 0.57

Author	Sample Size	Intervention	Stratified Median OS Months (95%CI)	HR (95%CI)	P-value
Ksienski et al.	271	Nivolumab 3mg/kg per 2 weeks Pembrolizumab 2mg/kg per 3 weeks	NR	Nivolumab Age (≥64 vs. <64): 0.83* (0.56-1.23)	0.352
Merino Almazan et al.	221	Nivolumab 3mg/kg per 2 weeks	Age <70: 9.7 (6.9-12.5) Age >70: 12.8 (3.4-22.3)	0.95 (0.61-1.49)	0.821
Montana et al.	98	Nivolumab 3 mg/kg per 2 weeks	Age <65: 5.72 (2.99-9.3) Age >65: 8.05 (4.11-15.78)	NR	0.24706
Sex					
Areses Manrique et al.	188	Nivolumab 3mg/kg per 2 weeks	Male: 14.8 (NR) Female: 10.6 (NR)	NR	0.23
Bagley et al.	175	Nivolumab 3mg/kg per 2 weeks	NR	Male vs. Female: 1.39 (0.9-2.1)	NR
Diem et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	Male vs. Female: 0.76* (0.25-2.32)	0.629
Dudnik et al.	260	Nivolumab 3mg/kg per 2 weeks	Male: 6.2 (4.5-8.4) Female: 5.6 (4.3-10.7)	1.16* (0.79-1.69)	0.43
Dumenil et al.	67	Nivolumab 3mg/kg per 2 weeks	NR	Male vs. Female: 1.25 (0.68-2.31)	0.475
Facchinetti et al.	54	Nivolumab 3mg/kg per 2 weeks	Male: 6.4 (2.9-9.9) Female: Not Reached	NR	0.388
Fukui et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	Male vs. Female: 1.37 (0.54-3.43)	0.51
Garde-Noguera et al.	175	Nivolumab 3mg/kg per 2 weeks	Male: 5.4 (NR) Female: 11.3 (NR)	NR	0.52
Grossi et al.	371	Nivolumab 3mg/kg per 2 weeks	NR	Male vs. Female: 1.67 (1.05-2.64)	0.03
Ksienski et al.	271	Nivolumab:	NR	Nivolumab:	0.224

Author	Sample Size	Intervention	Stratified Median OS Months (95%CI)	HR (95%CI)	P-value
		3mg/kg per 2 weeks Pembrolizumab: 2mg/kg per 3 weeks		Male vs. Female: 1.27* (0.86-1.87)	
Lesueur et al.	104	Nivolumab 3mg/kg per 2 weeks	NR	0.85 (0.55-0.62)	0.845
Merino Almazan et al.	221	Nivolumab 3mg/kg per 2 weeks	Male: 9.5 (4.9-14.2) Female: 11.8 (6.5-17.0)	0.76 (0.44-1.32)	0.326
Montana et al.	98	Nivolumab 3 mg/kg per 2 weeks	Male: 6.87 (3.81–10.98) Female: 5.72 (3.09–14.1)	NR	0.58093
Schouten et al.	248	Nivolumab 3 mg/kg per 2 weeks	Male: 8.1 (4.78-11.42) Female: 13.1 (Not Reached)	0.968* (0.62-1.51)	0.886
ECOG-PS					
Areses Manrique et al.	188	Nivolumab 3mg/kg per 2 weeks	ECOG 0: Not Reached ECOG 1: 11.79 (8.5-15) ECOG 2: 3.4 (2.3-4.4)	NR	0.006
Bagley et al.	175	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (≥2 vs. <2): 2.49* (1.6-3.9)	NR
Diem et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (score not specified): 1.47* (0.72-3.01)	0.287
Dudnik et al.	260	Nivolumab 3mg/kg per 2 weeks	ECOG 0-1: 9.5 (6.7-Not Reached) ECOG ≥2: 3.5 (2.6-4.5)	HR: 1.86* (1.31-2.65)	0.0006
Dumenil et al.	67	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (2 at start of nivolumab therapy): 2.20* (0.89-5.42)	0.086
Facchinetti et al.	54	Nivolumab 3mg/kg per 2 weeks	ECOG 0-1: 17.7 (NR) ECOG 2: 1.8 (0-3.8)	3.86* (1.66-9.02)	0.002
Fiorica et al.	35	Nivolumab	NR	ECOG (2 vs <2):	0.001

Author	Sample Size	Intervention	Stratified Median OS Months (95%CI)	HR (95%CI)	P-value
		3mg/kg per 2 weeks		8.8 (3.08-25.18)	
Fukui et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (0 vs. 1-3): 1.64* (0.43-6.25)	0.47
Garde-Noguera et al.	175	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (0-1 vs. 2): 0.62* (0.36-1.04)	0.073
Grossi et al.	371	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (2 vs. 0-1): 1.69 (0.94-3.05)	0.08
Juergens et al.	472	Nivolumab 3 mg/kg per 2 weeks	ECOG 0-1: 12.9 (11.2-15.5) ECOG 2: 6.8 (4.2-13.9)	1.64* (1.11-2.43)	0.01
Ksienski et al.	271	Nivolumab 3mg/kg per 2 weeks Pembrolizumab 2mg/kg per 3 weeks	NR	Nivolumab ECOG (≥2 vs. 0/1): 2.76* (1.86-4.10)	<0.001
Lesueur et al.	104	Nivolumab 3mg/kg per 2 weeks	NR	ECOG PS >1: 1.81* (0.96-3.42)	0.07
Merino Almazan et al.	221	Nivolumab 3mg/kg per 2 weeks	ECOG 0-1: 12.8 (9.5-16.1) ECOG 2: 2.9 (0.2-5.6)	0.29* (0.18-0.467)	<.0001
Montana et al.	98	Nivolumab 3 mg/kg per 2 weeks	ECOG 0: 11.96 (9.3-NE) ECOG 1: 8.05 (5.75-14.1) ECOG ≥2: 3.09 (2.37-6.21)	NR	0.00421
Schouten et al.	248	Nivolumab 3 mg/kg per 2 weeks	ECOG <2: 12.5 (8.91-16.09) ECOG ≥2: 4.5 (2.08-6.92)	2.4* (1.34-4.31)	0.003
Tournoy et al.	267	Nivolumab	ECOG 0: Not Reached ECOG 1: 7.3 (5.3-9.2) ECOG 2: 3.6 (2.9-4.3)	NR	<.00001
Histology					
Areses Manrique et al.	188	Nivolumab 3mg/kg per 2 weeks	Squamous: 14.8 (NR)	NR	0.74

Author	Sample Size	Intervention	Stratified Median OS Months (95%CI)	HR (95%CI)	P-value
			Non-squamous: 11.7 (NR)		
Bagley et al.	175	Nivolumab 3mg/kg per 2 weeks	NR	Non-squamous vs. Squamous: 1.18 (0.7-1.9)	NR
Costantini et al.	303	Nivolumab 3mg/kg per 2 weeks	Squamous: 8.5 (6.3-13.5) Non-squamous: 12.1 (8.1-15.1)	1.47 (0.96-2.27)	0.079
Diem et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	Squamous vs. Non-squamous: 0.40* (0.11-1.41)	0.153
Dudnik et al.	260	Nivolumab 3mg/kg per 2 weeks	Squamous: 6.1 (4.0-8.6) Non-squamous: 5.8 (4.5-8.6)	1.12* (0.73-1.70)	0.61
Dumenil et al.	67	Nivolumab 3mg/kg per 2 weeks	NR	Squamous vs. Adenocarcinoma: 1.38* (0.62-3.12)	0.432
Facchinetti et al.	54	Nivolumab 3mg/kg per 2 weeks	Squamous: 5.5 (NR) Adenocarcinoma: 6.6 (4.7-8.5)	NR	0.724
Fiorica et al.	35	Nivolumab 3mg/kg per 2 weeks	NR	Squamous vs. Non-squamous: 0.94 (0.39-2.28)	0.898
Fukui et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	Non-squamous vs. Squamous: 0.77 (0.28-2.12)	0.61
Garde-Noguera et al.	175	Nivolumab 3mg/kg per 2 weeks	Squamous: 5.7 (NR) Non-squamous: 7.1 (NR)	NR	0.332
Juergens et al.	472	Nivolumab 3 mg/kg per 2 weeks	Squamous: 13.10 (8.61-NA) Non-squamous: 11.80 (10.45-14.10)	0.95* (0.72-1.26)	0.71
Ksienski et al.	271	Nivolumab 3mg/kg per 2 weeks Pembrolizumab 2mg/kg per 3 weeks	Nivolumab: Squamous: 12.9 (5.6-Not Reached) Non-squamous: 8.5 (7.1-10.7)	Nivolumab (squamous vs. non-squamous): 0.82* (0.48-1.39)	0.459

Author	Sample Size	Intervention	Stratified Median OS Months (95%CI)	HR (95%CI)	P-value
Lesueur et al.	104	Nivolumab 3mg/kg per 2 weeks	NR	Histology: 0.78 (0.48-1.24)	0.565
Merino Almazan et al.	221	Nivolumab 3mg/kg per 2 weeks	Squamous: 6.9 (3.6-10.2) Non-squamous: 12.8 (7.8-17.9)	0.59* (0.38-0.91)	0.019
Schouten et al.	248	Nivolumab 3 mg/kg per 2 weeks	Squamous: Not Reached Non-squamous: 7.8 (3.67-11.93)	0.47* (0.25-0.91)	0.026

CI – Confidence Interval; OS - Overall Survival; HR – Hazard Ratio; ECOG PS – Eastern Cooperative Oncology Group Performance Status; NR – Not Reported; *- Adjusted HR

Appendix D. Summary of studies investigating the association between independent factors and progression-free survival associated with nivolumab.

Author	Sample Size	Intervention	Stratified Median PFS Months (95%CI)	HR (95%CI)	P-value
Age					
Bagley et al.	175	Nivolumab 3mg/kg per 2 weeks	NR	Age (<75): 1.29 (0.9-1.9)	NR
Diem et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	Age (per year): 0.96 (0.92-1.01)	0.091
Dumenil et al.	67	Nivolumab 3mg/kg per 2 weeks	NR	Age (<70 vs. ≥70 years): 1.01 (0.98-1.05)	0.539
Garde-Noguera et al.	175	Nivolumab 3mg/kg per 2 weeks	Age <70: 2.4 (NR) Age ≥70: 3.7 (NR)	NR	0.756
Grossi et al.	371	Nivolumab 3mg/kg per 2 weeks	Age <65: 4.0 (2.3-5.7) Age 65-<75: 4.5 (3.5-5.5) Age ≥75: 3.2 (1.1-5.3)	NR	NR
Merino Almazan et al.	221	Nivolumab 3mg/kg per 2 weeks	Age <70: 5.2 (3.2-7.2) Age >70: 5.1 (0.4-9.7)	0.92 (0.62-1.36)	0.662
Montana et al.	98	Nivolumab 3 mg/kg per 2 weeks	Age <65: 1.69 (1.64-2.73) Age >65: 2.27 (1.81-3.62)	NR	0.30332

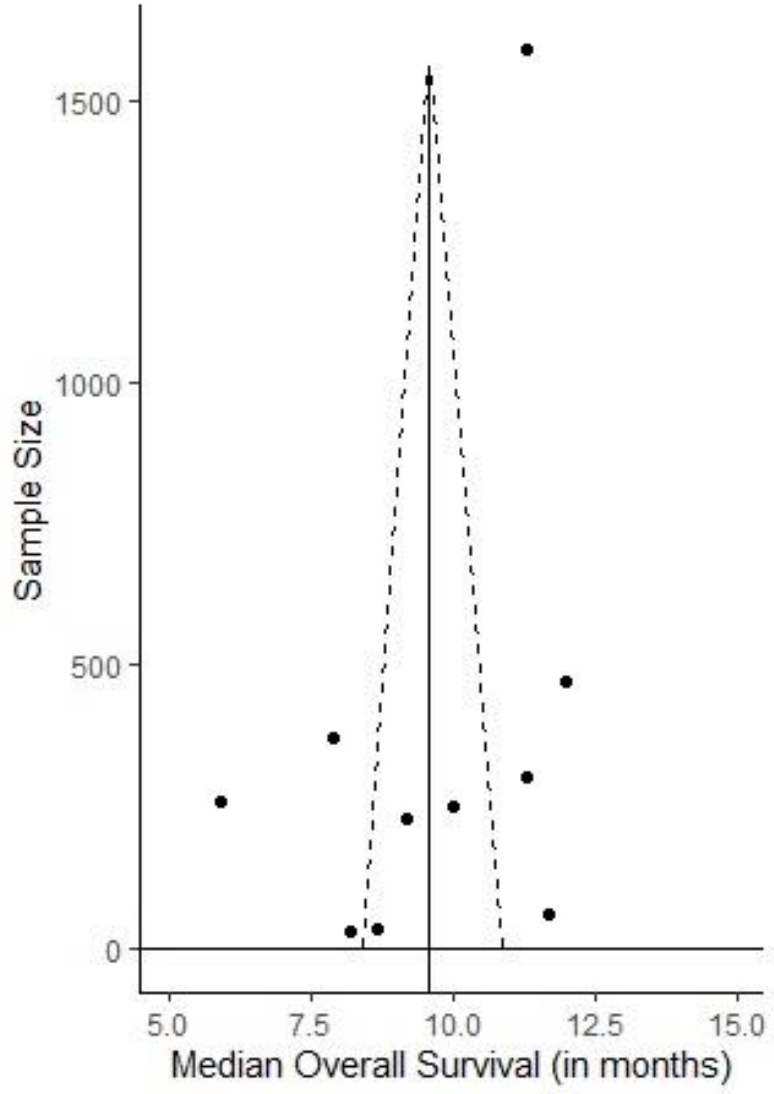
Author	Sample Size	Intervention	Stratified Median PFS Months (95%CI)	HR (95%CI)	P-value
Shiroyama et al.	201	Nivolumab 3mg/kg per 2 weeks	NR	Age (<75 years): 1.28 (0.87-1.89)	0.21
Sex					
Bagley et al.	175	Nivolumab 3mg/kg per 2 weeks	NR	Sex (Male): 1.41 (1.02-1.90)	NR
Diem et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	Sex (Male): 0.94* (0.42-2.11(	0.880
Dumenil et al.	67	Nivolumab 3mg/kg per 2 weeks	NR	Sex (Male): 0.85 (0.45-1.61)	0.609
Garde-Noguera et al.	175	Nivolumab 3mg/kg per 2 weeks	Male: 2.6 (NR) Female: 2.9 (NR)	NR	0.937
Lesueur et al.	104	Nivolumab 3mg/kg per 2 weeks	NR	Sex (Not Specified): 0.91 (0.59-1.41)	0.685
Merino Almazan et al.	221	Nivolumab 3mg/kg per 2 weeks	Male: 4.7 (3.2-6.2) Female: 9.6 (5.2-14.1)	0.72 (0.44-1.18)	0.191
Montana et al.	98	Nivolumab 3 mg/kg per 2 weeks	Male: 1.87 (1.71-3.52) Female: 1.68 (1.61-3.09)	NR	0.06133
Schouten et al.	248	Nivolumab 3 mg/kg per 2 weeks	Male: 2.5 (2.22-2.78) Female: 2.6 (1.79-3.41)	0.965* (0.67-1.38)	0.845
Shiroyama et al.	201	Nivolumab 3mg/kg per 2 weeks	NR	Sex (Female): 1.34 (0.97-1.85)	0.077
ECOG-PS					

Author	Sample Size	Intervention	Stratified Median PFS Months (95%CI)	HR (95%CI)	P-value
Bagley et al.	175	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (≥2 vs. 0/1): 1.89* (1.3-2.8)	NR
Diem et al.	52	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (at treatment start): 1.28* (0.82-1.98)	0.278
Dumenil et al.	67	Nivolumab 3mg/kg per 2 weeks	ECOG 0-1: 6.6 (IQR: 1.9-13.7) ECOG 2: 1.1 (IQR: 0.8-3.7)	5.17* (1.99-13.43)	0.001
Kataoka et al.	189	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (≥2 vs. 0/1): 1.94* (1.29-2.92)	0.003
Lesueur et al.	104	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (>1): 1.81* (0.96-3.42)	0.07
Merino Almazan et al.	221	Nivolumab 3mg/kg per 2 weeks	ECOG 0-1: 7.6 (5.2-9.9) ECOG 2: 1.9 (0.5-3.3)	3.94 (2.53-6.11)	<.0001
Montana et al.	98	Nivolumab 3 mg/kg per 2 weeks	ECOG 0: 2.27 (1.74-NE) ECOG 1: 2.0 (1.64-4.17) ECOG ≥2: 1.81 (1.64-2.73)	NR	0.15128
Schouten et al.	248	Nivolumab 3 mg/kg per 2 weeks	ECOG <2: 2.6 (2.16-3.04) ECOG ≥2: 2.1 (1.62-2.58)	1.25* (0.75-2.10)	0.396
Shiroyama et al.	201	Nivolumab 3mg/kg per 2 weeks	NR	ECOG (≥2): 1.60* (1.10-2.33)	0.013
Histology					

Author	Sample Size	Intervention	Stratified Median PFS Months (95%CI)	HR (95%CI)	P-value
Bagley et al.	175	Nivolumab 3mg/kg per 2 weeks	NR	Non-squamous: 1.3 (0.9-1.9)	NR
Costantini et al.	303	Nivolumab 3mg/kg per 2 weeks	Squamous: 2.9 (2.1-4.6) Non-squamous: 2.3 (1.9-3.5)	NR	NR
Dumenil et al.	67	Nivolumab 3mg/kg per 2 weeks	NR	Squamous vs. Adenocarcinoma: 1.46 (0.81-2.62)	0.211
Garde-Noguera et al.	175	Nivolumab 3mg/kg per 2 weeks	Squamous: 2.3 (NR) Non-squamous: 2.8 (NR)	NR	0.194
Lesueur et al.	104	Nivolumab 3mg/kg per 2 weeks	NR	Histology: 0.80 (0.55-1.14)	0.459
Kataoka et al.	189	Nivolumab 3mg/kg per 2 weeks	NR	Non-squamous: 0.91* (0.59-1.42)	0.68
Merino Almazan et al.	221	Nivolumab 3mg/kg per 2 weeks	Squamous: 4.7 (2.7-6.8) Non-squamous: 6.1 (2.9-9.3)	0.79 (0.55-1.14)	0.212
Schouten et al.	248	Nivolumab 3 mg/kg per 2 weeks	Squamous: 2.8 (1.01-4.59) Non-squamous: 2.4 (2.16-2.64)	0.81* (0.50-1.31)	0.388
Shiroyama et al.	201	Nivolumab 3mg/kg per 2 weeks	NR	Squamous: 1.25 (0.85-1.83)	0.26

CI – Confidence Interval; OS - Overall Survival; HR – Hazard Ratio; ECOG PS – Eastern Cooperative Oncology Group Performance Status; NR – Not Reported; *- Adjusted HR

Appendix E. Funnel Plot of median overall survival associated with nivolumab



Appendix F. GRADE table for overall survival and progression-free survival associated with nivolumab.

Certainty assessment							Number of patients		Effectiveness (95% CI)	Certainty
№ of Studies	Study Design	Risk of Bias	Inconsistency	Indirectness	Imprecision	Other Considerations	Nivolumab	No Comparator		
Overall Survival										
10	observational studies	not serious	very serious [a,b]	not serious	not serious	publication bias strongly suspected [c]	3594	-	9.6 months (8.4 – 10.9)	⊕◯◯◯ VERY LOW
Progression-free Survival										
5	observational studies	not serious	very serious [a,b,d]	not serious	not serious	Insufficient number of studies to assess the presence of publication bias	1140	-	2.6 months (1.6 – 3.6)	⊕◯◯◯ VERY LOW

CI: Confidence Interval
a. Some variance of point estimates across studies
b. Considerable statistical heterogeneity
c. Funnel plot suggests presence of publication bias
d. Minimal overlap of confidence intervals

Appendix G. Net Benefit Estimates for Afatinib versus Gefitinib – LY

Covariates NB (95% CI)	Net Benefits λ = 0		Net Benefits λ = 20000		Net Benefits λ = 50000		Net Benefits λ = 100000	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
Constant Term	-125950 (-133886--118013)	-257218 (-336392--178043)	-93842 (-100959--86726)	-185896 (-257515--114276)	-45681 (-53102--38260)	-78913 (-150569--7256)	34587 (23468-45707)	99392 (827-197958)
Covariates								
Afatinib	5809 (-9662-21280)	-9745 (-22230-2739)	8224 (-5649-22096)	-4157 (-15451-7136)	11846 (-2620-26312)	4225 (-7074-15524)	17883 (-3792-39559)	18195 (2653-33737)***
Year of diagnosis		64164 (48585-79744)*		49113 (35020-63206)*		26537 (12437-40637)*		-11091 (-30486-8304)
Age		-4266 (-10656-2123)		-5832 (-11612--52)***		-8181 (-13964--2398)**		-12095 (-20050--4140)**
Female Sex		7957 (-4948-20861)		10767 (-906-22440)		14983 (3304-26662)***		22009 (5944-38073)**
Urban versus Rural		2907 (-16663-22477)		-334 (-18036-17369)		-5195 (-22906-12517)		-13296 (-37659-11066)
Neighborhood Income		570 (-5475-6615)		-506 (-5974-4962)		-2120 (-7591-3351)		-4810 (-12335-2716)
Geographical Residency		-463 (-5059-4132)		-175 (-4332-3982)		258 (-3901-4417)		979 (-4742-6700)
Clinical Stage		17389 (-4684-39462)		11560 (-8407-31527)		2816 (-17161-22794)		-11756 (-39235-15723)
Comorbidity		13420 (-7261-34101)		7197 (-11510-25904)		-2137 (-20854-16580)		-17695 (-43440-8051)
Bone Metastasis		-16232 (-31394--1071)***		-15212 (-28927--1497)***		-13682 (-27404-40)		-11131 (-30006-7744)
Liver Metastasis		-11432 (-36192-13329)		-10585 (-32982-11813)		-9314 (-31723-13096)		-7196 (-38020-23629)
Lung Metastasis		2319 (-15924-20562)		3429 (-13073-19931)		5094 (-11417-21604)		7868 (-14843-30579)
Brain Metastasis		-21796 (-39069--4523)***		-21724 (-37349--6099)**		-21616 (-37249--5983)**		-21436 (-42939-67)
R-squared (adjusted)	0.0011	0.4274	0.0009	0.3826	0.0038	0.2339	0.0039	0.0572

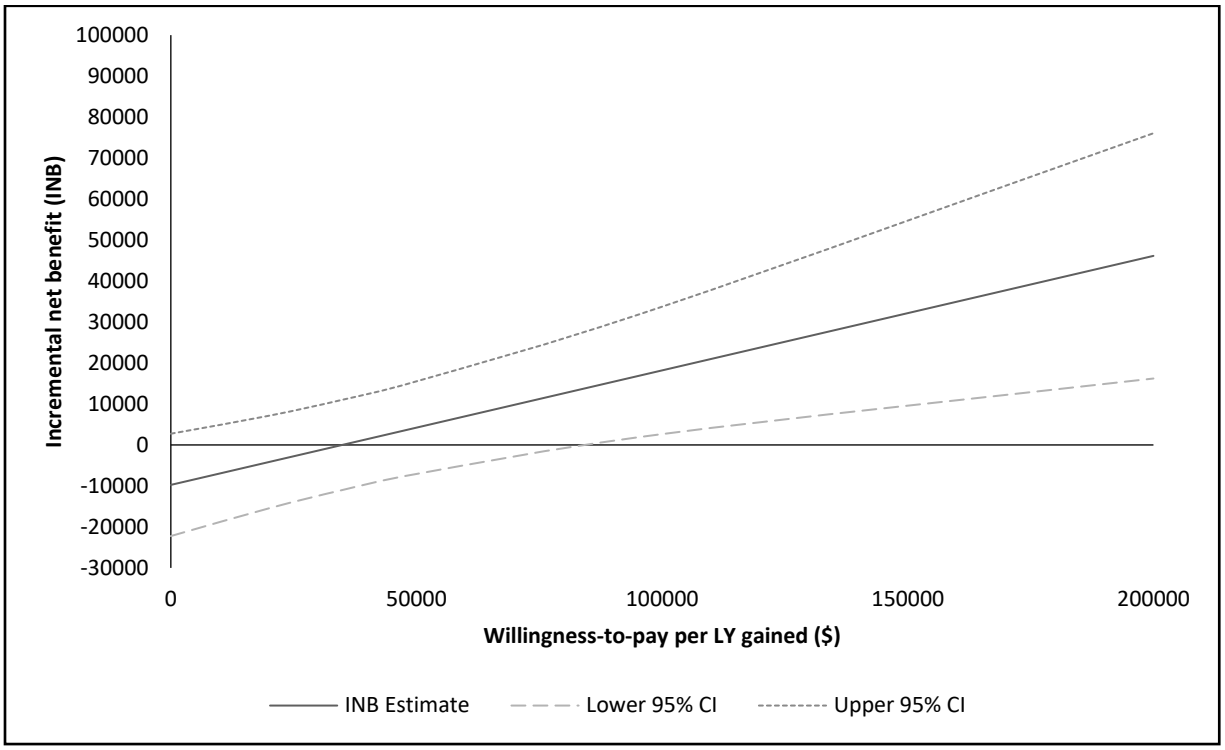
***p<.05; **p<.01; *p<.001; CI: Confidence Interval

Appendix H. Estimates of Incremental Net Benefit and Probability of Cost-Effectiveness of Afatinib, Erlotinib, and Gefitinib - LY

λ Threshold	Afatinib Versus Gefitinib			Afatinib Versus Erlotinib			Gefitinib Versus Erlotinib		
	INB Estimate (SE)	P-value	Probability of Cost-effectiveness	INB Estimate (SE)	P-value	Probability of Cost-effectiveness	INB Estimate (SE)	P-value	Probability of Cost-effectiveness
$0	-9745 (6350)	0.126	0.022	1549 (10948)	0.888	0.703	13610 (9458)	0.151	0.919
$10,000	-6951 (5994)	0.247	0.040	8566 (10140)	0.399	0.892	16144 (8955)	0.072	0.984
$20,000	-4157 (5744)	0.470	0.095	15583 (9487)	0.102	0.987	18678 (8579)	0.030	0.998
$30,000	-1363 (5616)	0.808	0.209	22600 (9025)	0.013	1.000	21213 (8345)	0.011	1.000
$40,000	1431 (5617(	0.799	0.402	29616 (8783)	0.001	1.000	23747 (8266)	0.004	1.000
$50,000	4225 (5747)	0.463	0.602	36633 (8780)	<.001	1.000	26281 (8346)	0.002	1.000
$60,000	7019 (5999)	0.243	0.752	43650 (9015)	<.001	1.000	28816 (8581)	0.001	1.000
$70,000	9813 (6357)	0.123	0.865	50667 (9471)	<.001	1.000	31350 (8959)	0.001	1.000
$80,000	12607 (6804)	0.065	0.927	57684 (10118)	<.001	1.000	33884 (9462)	<.001	1.000
$90,000	15401 (7326)	0.036	0.958	64701 (10922)	<.001	1.000	36419 (10073)	<.001	1.000
$100,000	18195 (7906)	0.022	0.974	71718 (11851)	<.001	1.000	38953 (10772)	<.001	1.000
$150,000	32165 (11346)	0.005	0.992	106803 (17605)	<.001	1.000	51624 (15118)	<.001	1.000
$200,000	46135 (15222)	0.003	0.995	141888 (24199)	<.001	1.000	64296 (20181)	0.002	1.000

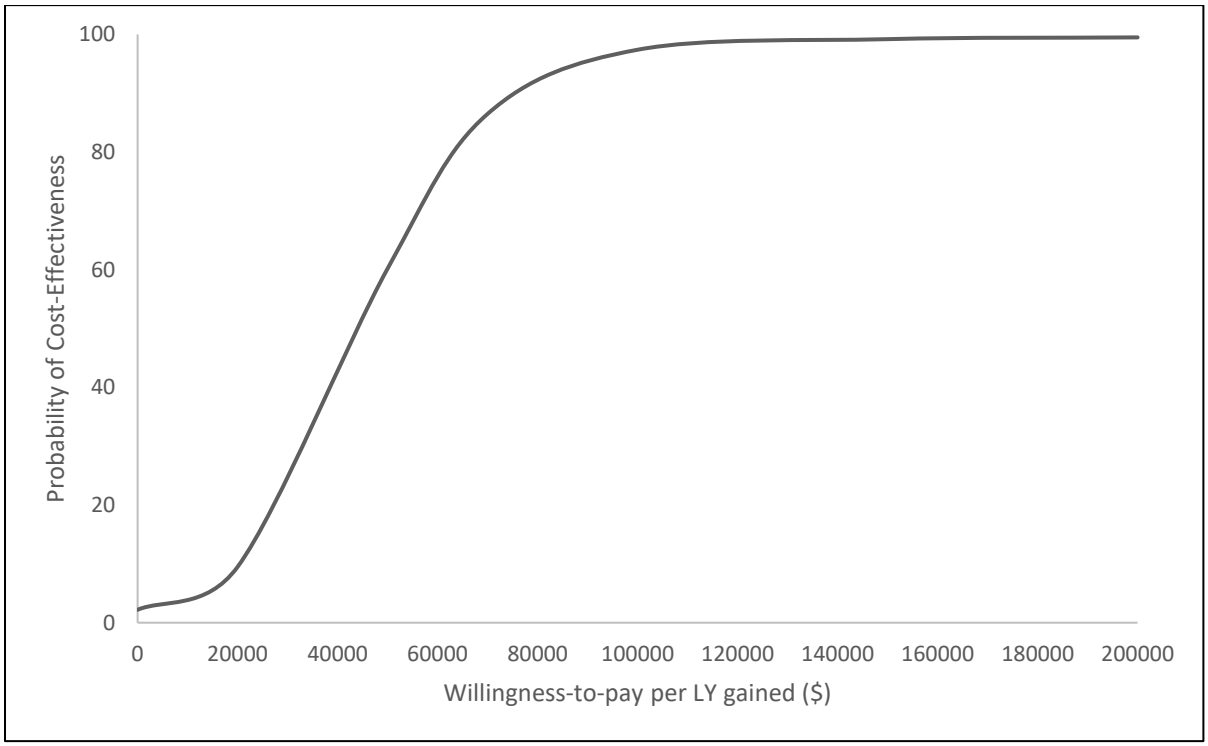
INB: Incremental Net Benefit; SE: Standard Error

Appendix I. Incremental Net Benefit by Willingness-To-Pay for Afatinib versus Gefitinib - LY



LY: Life Year

Appendix J. Cost Effectiveness Acceptability Curve for Afatinib versus Gefitinib - LY



LY: Life Year