Original Article

Second and later-line erlotinib use in non-small cell lung cancer: real world outcomes and practice patterns overtime in Canada

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Background: In Canada, epidermal growth factor receptor (EGFR) inhibitor therapies in advanced non-small cell lung cancer (NSCLC) were initially approved regardless of *EGFR* status. The purpose of this study is to characterise the use of second or later-line erlotinib therapy in Ontario, Canada from 2007–2016, as well as evaluate the impact of erlotinib therapy on survival and emergency department (ED) visits in a real-world population.

Methods: This is a retrospective cohort study derived at ICES (formerly known as the Institute for Clinical and Evaluative Sciences) of advanced NSCLC patients diagnosed from 2007–2016 in Ontario, Canada, over the age of 65, who received at least one dose of first-line chemotherapy. The exposure of interest was receipt of second or later-line erlotinib. The primary outcome was the hazard ratio for mortality evaluated using a Cox proportional hazards model, and the secondary outcome, ED visits, was evaluated using a Poisson model.

Results: First-line chemotherapy was administered in 30.4% of stage IV NSCLC patients. Of these patients, 19.7% received second or later-line erlotinib. The proportion of patients prescribed second or later-line erlotinib decreased over the course of the study (P<0.0001). Unadjusted median overall survival in the entire cohort was 325 days (95% CI: 314–337 days), 513 days (95% CI: 485–539 days) in the erlotinib cohort, and 282 days (95% CI: 270–291 days) in the non-erlotinib cohort. Despite this, the adjusted hazard ratio for death was 1.89 (95% CI: 1.73–2.07, P<0.0001) for patients on erlotinib. Patients receiving erlotinib also had a marginally higher relative rates of ED visits with an adjusted relative risk of 1.10 (95% CI: 1.02–1.19, P=0.013).

Conclusions: This study highlights the importance of using EGFR targeted treatments in NSCLC patients with a predictive biomarker, and suggests that treatment with erlotinib therapy is unlikely to benefit unselected patients with advanced NSCLC.

Keywords: Lung cancer; biomarkers; erlotinib; real-world data

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Introduction

Treatment of advanced non-small cell lung cancer (NSCLC) prior to 2009 consisted of an algorithm that contained of one or two lines of chemotherapy followed by best supportive care or erlotinib, a targeted inhibitor that was developed for use in the general lung cancer population. Erlotinib is a reversible ERBB1 receptor inhibitor that is postulated to work in many cancers due to its anti-proliferative effects through the inhibition of the epidermal growth factor receptor (EGFR) pathway (1,2). In 2005, Shepherd *et al.* published a randomized controlled trial of erlotinib monotherapy after first or second-line chemotherapy in patients with stage IV NSCLC. Erlotinib treatment in this setting yielded a 2-month improvement in overall survival (OS) (hazard ratio, 0.70; P<0.001) and became the internationally recognized standard of care (3). At the same time, early clinical and preclinical data emerged suggesting that patients with a mutation in the EGFR gene had dramatic responses to EGFR targeted therapy, with improved overall response rate and duration of response than patients without (4-6). This was confirmed in 2009 with the publication of the Iressa Pan Asian Study (IPASS) by Mok *et al.* revealing that *EGFR* mutations are a predictive biomarker for response to EGFR kinase inhibitors (7). Since the IPASS study, multiple EGFR inhibitors (first, second and third-generation) have been developed and established as standard first-line therapy in patients whose tumors harbor an activating *EGFR* mutation (8-13).

The prevalence of *EGFR* mutations in advanced NSCLC is variable depending on the geographical region and ethnicity of the patient. In patients with adenocarcinoma histology and of Asian ethnicity, prevalence can be as high as 50%, compared 15–20% in Caucasians (14,15). The Canadian population is comprised of many different ethnicities and *EGFR* mutation rates occur in approximately 20.6% of non-squamous patients (16). Testing for the *EGFR* mutation has evolved overtime in Canada. In Ontario, Canada testing for the *EGFR* mutation began in 2010, and reflex testing at the level of the pathologist for *EGFR* mutations in non-squamous NSCLC has been implemented between 2011–2014 in most centers (17). In 2015, the prevalence of *EGFR* mutation testing was approximately 72% for advanced non-squamous NSCLC patients at one institution in Ontario, Canada (18).

Erlotinib is approved and continues to be funded in Ontario as second or later-line monotherapy in stage IV adenocarcinoma regardless of whether or not a predictive *EGFR* mutation is present (19). In Canada, other approvals in the wild-type population are for afatinib as second line treatment in squamous histology and erlotinib as maintenance therapy post platinum doublet (20,21). Neither of these two regimens are funded by the public payer in Ontario. The indication for erlotinib as second or third-line therapy in wild-type NSCLC has been de-listed by the U.S. Food and Drug Administration (FDA) after the IUNO trial failed to demonstrate improvement in OS or PFS when erlotinib was used as maintenance therapy post platinum-doublet chemotherapy in patients without tumor *EGFR* mutations (22,23). *EGFR* mutation testing became standard of care in Ontario by 2011 (24,25). Real-world data on the efficacy of this therapy in unselected patients and *EGFR* wild-type patients has yielded conflicting results (26-32). The uptake and patient outcomes of erlotinib as later-line treatment since *EGFR* testing has been in place in Ontario, Canada is unknown. The purpose of this study was to characterize the use of second or later-line erlotinib therapy in Ontario from 2007–2016, as well as evaluate the impact of erlotinib therapy on survival and emergency department (ED) visits in a real-world population.

We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/jtd-21-804).

Methods

Study design and data sources

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Research Ethics Board of the Princess Margaret Cancer Centre/University Health Network, Toronto, Canada (REB: 19-5286) and individual consent for this retrospective analysis was waived.

This was a retrospective cohort study designed to explore the effect of second or later-line erlotinib on survival in advanced NSCLC. The cohort was restricted to patients in Ontario, Canada, with a valid health card, over the age of 65. This cohort was derived at ICES (formerly known as the Institute for Clinical and Evaluative Sciences). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Ontario health care is delivered by a single payer and patients' unique Ontario Health Insurance

Plan (OHIP) numbers can be linked to various databases containing information on health system encounters, diagnoses, and (for patients over the age of 65) prescription drugs. Provincial datasets used for this study include Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), Ontario Cancer Registry (OCR), Registered Persons Database (RPDB), Ontario Disability Benefit (ODB), Ontario Health Insurance Plan Claims Database (OHIP), Continuing Care Reporting System (CCRS), Ontario Mental Health Reporting System (OMHRS), National Ambulatory Care Reporting System (NACRS), Local Health Integration Network (LHIN), Drugs List (DIN), Congestive Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), Ontario Diabetes Dataset (ODD), New Drug Funding Program (NDFP), Surname Based Ethnicity Group (ETHNIC), Ontario Dementia Database (DEMENTIA). These datasets were linked using unique encoded identifiers and analyzed at ICES.

Cohort

Our cohort was comprised of all patients with valid public health insurance, aged 65 years or older and diagnosed with advanced NSCLC (defined using relevant diagnosis codes from the International Classification of Diseases, revision 10, with disease AJCC 8th edition stage IIIB/IV). Patients that completed first line chemotherapy in Ontario, Canada between 1/1/2007 and 12/31/2016 were included, and entered the cohort on the last date of first-line chemotherapy administration.

Patients were excluded if: first-line chemotherapy did not contain any of vinorelbine, gemcitabine, paclitaxel, or pemetrexed; second-line chemotherapy that did not contain any of docetaxel, pemetrexed, nivolumab, pembrolizumab, gemcitabine; another cancer diagnosis was made in the 5 years preceding their lung cancer diagnosis or during follow up; they received chemotherapy prior to their diagnosis of lung cancer; they were >105 years of age at the time of diagnosis (per standard protocol); died on the cohort entry date; received erlotinib prior to the cohort entry date; or switched chemotherapy drugs four or more times.

Primary exposure

The primary exposure in the model was a time varying covariate of erlotinib exposure, in order to isolate for the effect of erlotinib and mitigate immortal person time bias. A prescription filled for erlotinib was considered an exposure.

Primary and secondary outcomes

The primary outcome was the hazard ratio for mortality in the cohort. Data on patient status was collected until death or study end (12/31/2018); 2007 was chosen as the first inclusion year as this is the initial year staging information was available in the administrative database, and 2016 as the last inclusion year as this would allow for at least 2 years of follow up. If patients were alive at the time of study end, they were censored. Overall survival of patients in the model was calculated from day of lung cancer diagnosis to date of death or censorship.

All cause ED visits were also evaluated and treated as a count variable during the follow up period.

Other covariates

Variables collected as potential covariates in the model included age at diagnosis, chemotherapy history (time varying), duration of first line chemotherapy, histology, aggregated diagnosis groups (ADG) score (reflecting comorbidities), socioeconomic status (SES), sex, and area of residence (LHIN), place of residence (urban *vs.* rural), ethnicity (if available), second-line chemotherapy drugs received, duration of second-line therapy, history of comorbidities [CHF, dementia, COPD, type II diabetes mellitus (DM)], year of cohort entry, time on erlotinib, and ICES unique identifier (IKN). First-line chemotherapy was defined as initial use of "vinorelbine, gemcitabine, paclitaxel, or pemetrexed" after diagnosis of advanced NSCLC. Concomitant use of a platinum agent is not systematically collected in the NDFP data, and was not available to us.

SES was estimated using income quintiles which are generated based on conversion of subjects' postal codes using Statistics Canada's Postal Code Conversion File and linkage to census data (33). Patient comorbidity at the time of diagnosis was estimated using the Johns Hopkins ACG System Version XX (Baltimore, MD, USA) using diagnostic codes from CIHI-DAD, OHIP, RPDB, OMHRS (34,35).

Statistical methods

Descriptive statistics were used for baseline characteristics, and Chi-square analysis was performed to evaluate differences between groups. A Cox proportional hazards model was used to model the effect of erlotinib treatment

on survival. To mitigate immortal person time bias, erlotinib therapy was treated as a two-level time varying covariate, and chemotherapy history was coded as three-level time varying covariate (post first-line, post second-line, post 3+ lines) within the model. Variables used in the model were initially chosen *a priori*. The final variables included erlotinib use (time dependent), age at diagnosis, sex, chemotherapy history (time dependent), duration of first-line chemotherapy, index year of entry into cohort, histological subtype, area of residence, SES, and ADG score. As *EGFR* mutation status is not captured in these databases, an analysis was performed to evaluate the hazard function for erlotinib use in the cohort of patients receiving erlotinib.

To assess ED visits for patients receiving erlotinib, a Poisson regression analysis was performed. Clustering within subjects was accounted for due to the recurring nature of ED visits for an individual. After univariable screening, variables included in the final Poisson model include erlotinib use (time dependent), age, year of cohort entry, area of residence, SES, and ADG score.

Missing data was dealt with using stepwise deletion. Missing data was only present for income quintile, all other data were complete. Patients were censored in the analysis if they were alive at the end of the follow up period, or if lost to follow up.

Results

Participants

From 1/1/2007–12/31/2016, 30,208 patients were diagnosed with stage IIIB or IV NSCLC in Ontario, Canada. Only 30.4% of patients received chemotherapy with pemetrexed, gemcitabine, paclitaxel or vinorelbine. These numbers are consistent with previously published data on rates of chemotherapy use in advanced NSCLC in Ontario (36). The final cohort consisted of 3,846 patients (*Figure 1*).

Of patients that received at least one dose of first-line chemotherapy, 19.7% received second or later-line erlotinib. Patients that received erlotinib were more likely to be female (46.5% *vs.* 42%), have no history of COPD (50.4% *vs.* 45.8%; *Table 1*). Gemcitabine (as a single agent or in combination with platinum) was the most commonly used agent in first-line in all groups. Use of pemetrexed in the first-line was more common in the non-erlotinib exposed group (18.7% *vs.* 10.8%), likely reflecting the increased use of pemetrexed and decreased use of erlotinib in later years. Patients treated with erlotinib were more likely to have received second-line chemotherapy (51.1% *vs.* 21.9%), and to have received 3 or more lines of chemotherapy (3.5% *vs.* 1.1%; *Table 1*). Median follow-up time for the entire cohort was 347 days (IQR 213–603 days).

Uptake of erlotinib therapy over time

The proportion of patients that were prescribed second or third-line erlotinib decreased over time (P<0.0001; *Figure 2*). In patients treated with erlotinib, the median time on erlotinib was 58 days (IQR 30–113 days) and the number of patients that received erlotinib for ≥90 days was 231 (30%), ≥180 days 98 (13%), and ≥365 days 42 (5%).

Primary outcome

Our primary outcome was to assess the effect of erlotinib use on survival in all patients with advanced NSCLC that received second or later-line erlotinib therapy. 96.5% of patients experienced the event of interest (death) during follow up, with 3.5% patients censored (3.3% at time of maximal follow-up, 0.2% at the time of lost OHIP). Unadjusted median overall survival in the entire cohort was 325 days (95% CI: 314–337 days). In the erlotinib and non-erlotinib cohort, the unadjusted median overall survival was 513 days (95% CI: 485–539 days) and 282 days (95% CI: 270–291 days) respectively.

Given the issue with immortal person time bias in our retrospective survival model, we included two time-dependent covariates (chemotherapy history and erlotinib use) to compare the hazard ratio for death of patients while on erlotinib therapy to those not on erlotinib therapy. This was performed so that the hazard ratio for death for patients on erlotinib could be interpreted in the context of those who have experienced the same lines of chemotherapy at the initiation of erlotinib. Due to the time-dependent nature of the covariates, only the adjusted and unadjusted hazard ratio for death for patients on erlotinib, and not the adjusted median overall survival, could be reported.

The unadjusted HR for death for patients on erlotinib therapy, conditional of having the same prior number of lines of chemotherapy was 1.86 (95% CI: 1.71–2.03, P<0.0001) and the adjusted HR for death was 1.89 (95% CI: 1.73–2.07, P<0.0001). Patients on erlotinib were 1.89-fold more likely to die than those not on erlotinib.

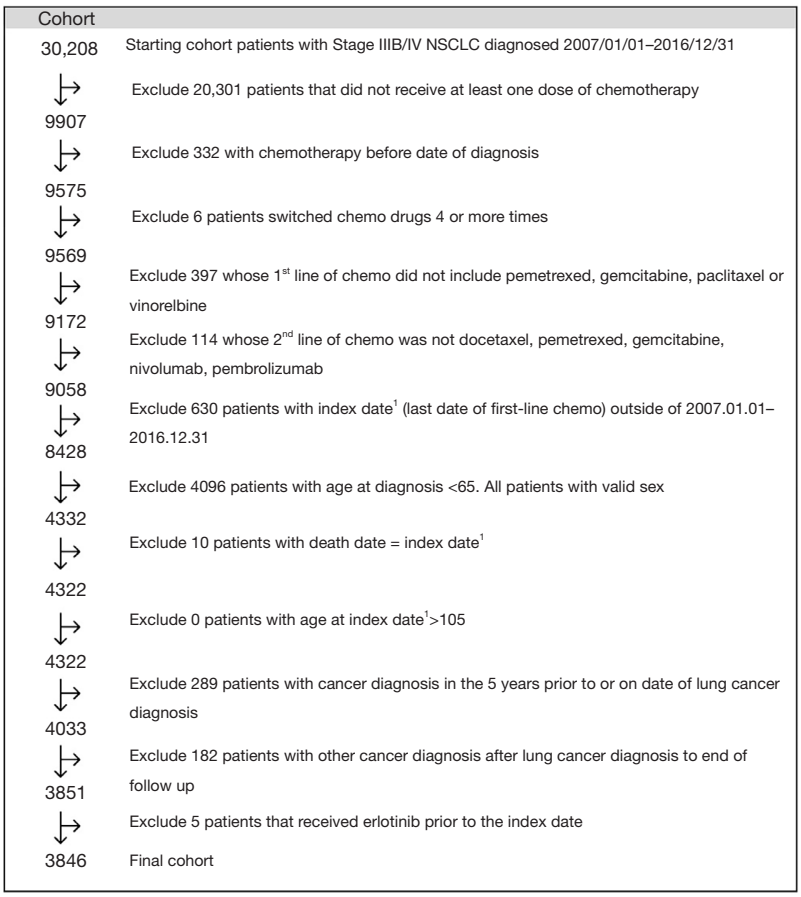

Figure 1 Cohort diagram of stage IIIB/IV NSCLC treated with at least one dose of chemotherapy after inclusion and exclusion criteria applied to the administrative databases. [1], index date is the last date of first line chemotherapy administration (cohort entry). NSCLC, non-small cell lung cancer.

We examined the hazard of mortality over time for patients that were treated with erlotinib during erlotinib therapy. We suspected a non-constant hazard function as the population exposed to erlotinib would be mixed, i.e., composed of *EGFR* positive (often untested) and wild type patients (as testing for *EGFR* was not funded in Ontario until 2014). In a mixed population, we would expect the hazard function to change over time. The hazard function for erlotinib treatment in our analysis changed over time, confirming the mixed population (*Figure 3*). For the first 89 days of erlotinib therapy, patients had an increasing hazard function, indicating worsening survival on erlotinib. However, if patients remained on erlotinib for longer than 89 days, their hazard function began to decrease, indicating improving survival on erlotinib, likely associated with *EGFR* mutant lung cancer.

Secondary outcome

In our cohort patients had a mean number of ED visits of 1.9 (SD 2.25) with a range of 0–42 visits. We examined the number of ED visits for patients on and off of erlotinib using a Poisson model with all-cause ED visits as the outcome. Erlotinib was treated as a time-dependent covariate, and other covariates in the model included age, year of cohort entry, area of residence, SES, and ADG score. During erlotinib treatment, patients receiving erlotinib had a marginally higher relative risk of ED visits. The unadjusted relative risk was 1.14 (95% CI: 1.05–1.23, P=0.0008) and the adjusted relative risk was 1.10 (95% CI: 1.02–1.19, P=0.013), compared to patients receiving either best supportive care or chemotherapy.

Table 1 Descriptive and treatment characteristics of patients that received at least one dose of first-line chemotherapy

Cohort characteristics	No erlotinib, % (n) (n=3,087)	Erlotinib, % (n) (n=759)
Sex		
Female	42 [1,296]	46.5 [353]
Male	58 [1,791]	53.5 [406]
Age at diagnosis (mean)	72 SD 5.2	72 SD 5.2
Stage		
IIIB	16.8 [520]	15.5 [118]
IV	83.2 [2,567]	84.5 [641]
Ethnicity		
Chinese	3.6 [110]	5.9 [45]
Unknown	95.8 [2,958]	93 [706]
South Asian	0.6 [19]	1.1 [8]
Histology		
Adenocarcinoma	55.9 [1,726]	58.5 [444]
Squamous	18.7 [578]	13.6 [103]
Large Cell	2.1 [64]	2.1 [16]
Other	23.3 [719]	25.8 [196]
Income quintile		
1	20.4 [628]	17.0 [129]
2	21.3 [656]	21.6 [164]
3	21 [646]	20.7 [157]
4	19.6 [601]	22.6 [170]
5	17.8 [544]	18.1 [137]
Missing	0.4 [14]	
Place of residence		
Urban	85.6 [2,640]	87.8 [661]
Rural	14.4 [446]	12.2 [93]
CHF	14.3 [442]	11.6 [88]
Dementia	2.2 [67]	1.6 [12]
COPD	54.2 [1,675]	49.6 [376]
Type II DM	30 [923]	31.7 [241]
ADG score		
0-4	4.4 [137]	4.3 [33]
5-9	24.7 [762]	25.8 [196]
10-14	46.8 [1,146]	48 [364]
15-19	22.4 [691]	20.1[157]
20+	1.7 [51]	1.3 [10]

Table 1 (*continued*)

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Cohort characteristics	No erlotinib, % (n) (n=3,087)	Erlotinib, % (n) (n=759)
Year of cohort entry		
2007	5.1 [157]	6.2 [47]
2008	8.9 [275]	13.2 [101]
2009	9.3 [287]	12.6 [95]
2010	10.4 [321]	13.4 [102]
2011	9.7 [300]	13.8 [105]
2012	9.7 [300]	11.3 [86]
2013	9.7[300]	10.3 [78]
2014	10.6 [328]	9.2 [70]
2015	13.3 [410]	5.4 [41]
2016	13.2 [409]	4.5 [34]
First-line chemotherapy		
Pemetrexed	18.7 [576]	10.8 [82]
Paclitaxel	15.7 [483]	17.5[133]
Gemcitabine	49.9 [1,540]	55.5 [421]
Vinorelbine	15.8 [488]	16.2 [123]
Second-line chemotherapy		
Total	21.9 [677]	51.1 [404]
Pemetrexed	60 [407]	69.8[282]
Pembrolizumab	<1.6 [<5]	<1.6 [<5]
Docetaxel	30.8 [208]	26.7 [108]
Gemcitabine	<8 [<25]	<1.4 [<11]
Nivolumab	1.2 [36]	<0.7 [<5]
Prior lines of chemotherapy		
1st line only	78.1 [2,410]	46.8 [355]
1st and 2nd line	20.8 [643]	49.6 [377]
3+ lines	1.1 [34]	3.6 [27]

Discussion

To our knowledge, this is the largest retrospective study of real-world second or later-line erlotinib use in unselected advanced NSCLC patients. Despite the longer crude survival difference in patients treated with erlotinib, the hazard for death suggests this difference was not attributable to erlotinib treatment, and rather the increased survival seen in the erlotinib group is reflective of the fact that these patients simply lived long enough to receive erlotinib. Review of the literature suggests marginal benefit of erlotinib therapy in the unselected or *EGFR* wild-type population. Many of those studies excluded patients who would typically be treated with erlotinib in the real world (e.g., those with brain metastases, poor performance status, organ dysfunction, recent radiation). However, these real-world patients are included in our analysis, which may account for the differences seen. Patients treated with erlotinib in our study also had higher relative risk of visiting the ED. This likely reflects increased healthcare utilization by advanced cancer patients receiving ongoing active

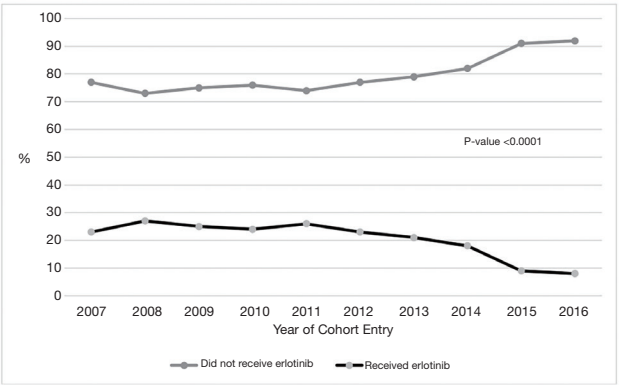

Figure 2 Proportion of patients in each cohort entry year by receipt of second or later-line erlotinib.

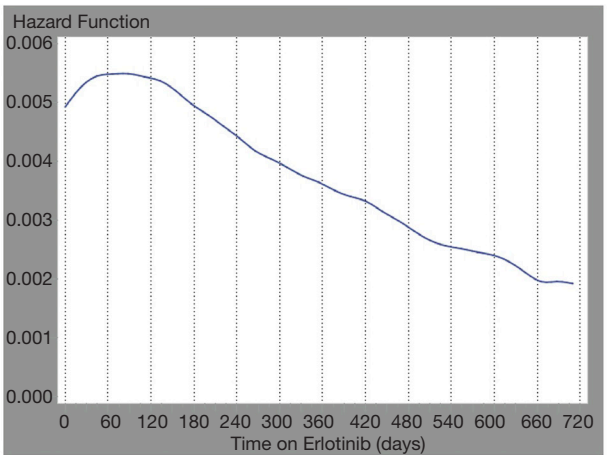

Figure 3 Hazard of mortality over time for patients that were treated with erlotinib while on erlotinib.

medical management at end of life, rather than erlotinib toxicity.

The landmark NCIC CTG BR.21 trial was designed and conducted in an era where EGFR targeted therapies were believed to benefit patients with EGFR protein expression, and activating *EGFR* mutations had not yet been discovered. This randomized trial of unselected patients receiving second or third-line erlotinib demonstrated an OS of 6.7 months compared to 4.7 months with placebo, respectively (hazard ratio, 0.70; P<0.001) (3). This important finding was reproduced in a phase IV registrational study of second-line erlotinib in unselected patients with a median OS Of 7.2 months (30). Other real-world studies of erlotinib in wild-type or unselected, pre-treated advanced NSCLC have not been as promising. A study of 54 patients with *EGFR* wild-type NSCLC treated with erlotinib after failure of second-line pemetrexed yielded a median survival of 5.8 months (95% CI: 3.3–8.6 months), with no responses seen (response rate 0%, 97.5% CI: 0.0–6.8%) (26). A French retrospective study demonstrated a survival benefit of 4.2 months (95% CI: 3.5–5.4 months) with erlotinib in unselected NSCLC patients, and 1.3 months (95% CI: 1.0–1.8) with supportive care, but this analysis did not account for immortal person time bias (32).

This study highlights the importance of using targeted therapy in a targeted fashion. The *EGFR* status was unknown in this patient population, and prior to 2011 was not routinely tested in Ontario, Canada. The study population therefore includes those with and without EGFR gene mutations. This is evidenced by the changing hazard function for erlotinib therapy based on duration of treatment. Initially the hazard function is positive, likely reflecting *EGFR* wild-type patients that are not deriving benefit. For patients receiving erlotinib for greater than 89 days, the hazard function decreases, likely accounting for the subset of patients with undiagnosed *EGFR* mutations experiencing substantial benefit (13% of cohort received erlotinib for >180 days).

Patients that received erlotinib therapy were more likely to be female, have adenocarcinoma histology, have received multiple lines of therapy, and were less likely to have COPD (often associated with smoking). This is an anticipated finding, as many of these factors portend a better prognosis in advanced NSCLC and these patients would be more likely to live to receive second or later-line therapy. The historical context of this study is important as during the study period, *EGFR* mutations were emerging as a predictive biomarker for *EGFR* targeted therapy. This is reflected in the decreasing proportion of patients receiving erlotinib as second- or third-line therapy over time, starting in 2011 after the publication of the IPASS trial (*Figure 1*). This is encouraging as it indicates physicians in Ontario rapidly change practice based on published high-level evidence and guidelines.

There are important limitations to this study. We are unable to identify which patients had an *EGFR* mutation as initially this was not tested, and in later years, although tested, is not captured in our databases. Ideally, we would be able to exclude those patients with *EGFR* mutations to understand the clinical outcomes of second or later-line erlotinib therapy in the *EGFR* wild-type population, which is representative of the current group for whom

this indication is still funded. We were also unable to verify whether patients received platinum, or the specific agent. We expect that most patients would have received a platinum agent in the first-line, as funding for pemetrexed, vinorelbine, paclitaxel in our study cohort would have required concomitant platinum administration. Imbalances in the use of cisplatin versus carboplatin could not be detected in our model, but we do not anticipate that this would impact on our findings. We used time varying covariates (chemotherapy and erlotinib use) in our models, however patient comorbidity score was not incorporated as a time varying covariate. Thus, the score at cohort entry was employed as a fixed value for simplicity in the analysis. Comorbidity is by nature time varying and changes in comorbidity over time were not accounted for. However, given the short life expectancy in this advanced lung cancer population, we do not anticipate changes from cohort entry nor impact on patient survival.

Our study suggests that treatment with erlotinib therapy is unlikely to benefit unselected patients with advanced NSCLC. While our study showed potential harm in this group, this finding must be tempered with the positive results of the phase III NCIC CTG BR.21 and the LUX-Lung 8 randomized trials (3,21). Also, the importance of under-genotyped patients must not be ignored – even today many advanced lung cancer patients in Canada have not been adequately genotyped for optimal therapy (16,37). Notwithstanding, our study highlights the importance of using targeted therapy in a targeted fashion, and the value of EGFR kinase inhibitor therapy in those with *EGFR* wild-type NSCLC is minimal at best.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/jtd-21-804

Data Sharing Statement: Available at https://dx.doi.org/10.21037/jtd-21-804

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/jtd-21-804). KP has received travel funding from Roche, continuing medical education speaker honorarium from Merck, Pfizer and Astra Zeneca, and consulting fees from Amgen. NBL has received continuing medical education speaker honoraria from Merck and Bristol Myers Squibb as well as institutional research funding from Array, Guardant Health, Pfizer, MSD, Roche, Astra Zeneca, Lilly, EMD Serono, Takeda, and Bayer. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Research Ethics Board of the Princess Margaret Cancer Centre/University Health Network, Toronto, Canada (REB: 19-5286) and individual consent for this retrospective analysis was waived.

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