Original Article

First-line osimertinib for patients with EGFR-mutated advanced non-small cell lung cancer: efficacy and safety during the COVID-19 pandemic

Suganija Lakkunarajah[1], Pauline T. Truong[1,2], Jeffrey N. Bone[3], Curtis Hughesman[4], Stephen Yip[4]^, Deepu Alex[4], Jason Hart[1,2], Philip Pollock[1], Sarah Egli[1], Melissa Clarkson[1], Mary Lesperance[5], Doran Ksienski[1,2]^

[1]BC Cancer-Victoria, British Columbia, Canada; [2]University of British Columbia, Victoria, British Columbia, Canada; [3]Biostatistics, Clinical Research Support Unit, BC Children's Hospital Research Institute, Vancouver, British Columbia, Canada; [4]BC Cancer-Vancouver, British Columbia, Canada; [5]University of Victoria, Department of Mathematics and Statistics, Victoria, British Columbia, Canada

Contributions: (I) Conception and design: S Lakkunarajah, D Ksienski, M Lesperance, JN Bone, PT Truong; (II) Administrative support: S Lakkunarajah, D Ksienski, S Egli, M Clarkson; (III) Provision of study materials or patients: S Yip, C Hughesman, D Alex, S Lakkunarajah, D Ksienski; (IV) Collection and assembly of data: S Yip, C Hughesman, D Alex, S Lakkunarajah, D Ksienski, J Hart, P Pollock; (V) Data analysis and interpretation: S Yip, C Hughesman, D Alex, S Lakkunarajah, JN Bone, PT Truong, D Ksienski, M Lesperance; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Doran Ksienski, MD, FRCPC, MPH. BC Cancer-Victoria, 2410 Lee Avenue V8R 6V5, Victoria, British Columbia, Canada; University of British Columbia, Victoria, British Columbia, Canada. Email: dksienski@bccancer.bc.ca.

Background: The FLAURA trial demonstrated improved overall survival (OS) with first-line osimertinib for patients with epidermal growth factor receptor (EGFR)-mutated advanced non-small cell lung cancer (NSCLC). We studied the efficacy and safety of osimertinib in a cohort treated during the coronavirus disease 2019 (COVID-19) pandemic.

Methods: Patients diagnosed with EGFR-mutated advanced NSCLC between 11 March 2020 to 31 December 2021 who received first-line osimertinib in British Columbia, Canada were identified retrospectively. Kaplan-Meier curves of OS and progression-free survival (PFS) from the start of osimertinib were plotted. The associations of baseline characteristics with PFS, and development of pneumonitis or dose reductions due to toxicity with OS were evaluated with hazard ratios estimated using univariable and multivariable Cox models.

Results: The cohort comprised 231 individuals. 58.7% of patients with *de novo* advanced NSCLC were initially diagnosed after presentation to the Emergency Room. At osimertinib initiation, 31.6% were aged ≥75 years and 45.5% had an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2. Median PFS and OS were 18.0 months [95% confidence interval (CI): 16.1–26.2] and 25.4 months (95% CI: 20.3–not reached), respectively. On multivariable analysis, age ≥75 years (*vs.* <75), ECOG PS 2/3 (*vs.* 0/1), ECOG PS 4 (*vs.* 0/1), current smokers (*vs.* never smokers), programmed death ligand 1 (PD-L1) expression ≥50% (*vs.* <1%), and L858R mutation (*vs.* exon 19 deletion) were associated with shorter PFS. Among 110 patients who progressed, 33.6% received subsequent therapy. A proportion of 16.5% of the cohort developed grade ≥3 adverse events. Pneumonitis from osimertinib (3.9% incidence) was weakly associated with shorter OS (hazard ratio: 2.59, 95% CI: 0.94–7.12, P=0.066); dose reductions were not associated with worse OS. 10.8% of patients developed COVID-19.

Conclusions: In a cohort receiving first-line osimertinib during the COVID-19 pandemic, ECOG PS ≥2 was observed in nearly half of patients at treatment initiation contributing to a median OS shorter than in FLAURA. The incidence of severe adverse events was low and dose reduction for drug toxicity did not

^ ORCID: Stephen Yip, 0000-0002-8514-9861; Doran Ksienski, 0000-0001-6300-8294.

impact OS. Identifying and reducing barriers to the diagnosis of NSCLC during the COVID-19 pandemic are required.

Keywords: Osimertinib; lung cancer; epidermal growth factor receptor (EGFR); survival; COVID-19

Submitted Feb 08, 2023. Accepted for publication Jul 04, 2023. Published online Jul 21, 2023.
doi: 10.21037/tlcr-23-81
View this article at: https://dx.doi.org/10.21037/tlcr-23-81

Introduction

Routine use of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI) in clinical practice has markedly improved prognosis for a subset of patients with advanced non-small cell lung cancer (NSCLC). EGFR mutations occur in approximately 48% of Asian and 19% of Western patients with NSCLC (adenocarcinoma histology) (1). The most common EGFR mutations are exon 19 deletion (19del) and exon 21 p.Leu858Arg (L858R) mutation. First generation EGFR TKI such as erlotinib and gefitinib improve median progression-free survival (PFS) compared to chemotherapy (11.0 *vs.* 5.6 months) as an initial treatment for EGFR-mutated advanced NSCLC (2).

Osimertinib is an orally administered third generation, irreversible EGFR TKI with marked activity in the central nervous system. The practice-changing phase III FLAURA trial demonstrated superior median PFS (18.9 *vs.* 10.2 months) and median overall survival (OS, 38.6 *vs.* 31.8 months) in previously untreated patients with advanced NSCLC harboring exon 19del or L858R mutations (3). Importantly, rates for grade ≥3 adverse events were lower with osimertinib than first generation EGFR TKI (34% *vs.* 45%) as well as drug toxicity leading to treatment discontinuation (13% *vs.* 18%).

Despite impressive gains in OS and PFS with osimertinib observed in the FLAURA study, knowledge gaps exist regarding drug efficacy and safety in routine clinical practice. For example, only individuals with Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 were included in FLAURA even though about 34–42% of patients with advanced NSCLC have ECOG performance status ≥2 at diagnosis (4,5). Inoue *et al.* conducted a phase II study of gefitinib for patients with EGFR-mutated advanced NSCLC who did not qualify for chemotherapy due to poor ECOG performance status (6). Impressively, most patients with a baseline ECOG performance status of 3–4 experienced marked improvements in performance status with gefitinib therapy and median OS in the entire cohort was 17.8 months. A prospective observational study of osimertinib in a similar patient population by Igawa *et al.* (n=16) noted significant improvements in ECOG performance status amongst half of the participants (7); however, the need for dose reduction due to adverse events and incidence of interstitial lung disease were numerically higher than in FLAURA.

At the onset of the coronavirus disease 2019 (COVID-19) pandemic, clinical practice guidelines strongly recommended against disruptions in the care of individuals with actionable mutations (8). However, frequent contacts with the healthcare system required for cancer diagnosis and treatments, can increase the risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure and infection. Moreover, patients with lung cancer who develop COVID-19 are at significant risk of hospitalization and mortality (9). To our knowledge, few real-world studies

Highlight box

Key findings

- In a cohort receiving first-line Osimertinib for EGFR-mutated advanced non-small cell lung cancer (NSCLC) during the COVID-19 pandemic, presentation to the Emergency Room with *de novo* advanced disease was common.
- 46% of patients had a poor ECOG performance status at treatment initiation.
- Age, ECOG performance status, smoking history, tumoral PD-L1 expression, and mutation type were all associated with progression free survival (PFS).
- The incidence of severe adverse events was low (17%).

What is known and what is new

- Osimertinib is recommended as an initial treatment for EGFR-mutated advanced NSCLC but uncertainty exists regarding efficacy and safety in routine clinical practice.
- In this study, median overall survival was likely lower than in the FLAURA trial due to the high proportion of patients with poor ECOG performance status.

What is the implication and what should change now?

- Given disruptions in cancer care due to the COVID-19 pandemic, efforts to minimize delays in NSCLC diagnosis are essential.

have described the incidence, severity, and management of COVID-19 in advanced NSCLC patients who were prescribed first-line osimertinib.

In this multicenter retrospective study, we evaluated survival outcomes relative to baseline clinical characteristics amongst patients receiving osimertinib as an initial treatment for EGFR-mutated (19del and L858R) advanced NSCLC during the COVID-19 pandemic. In addition, we investigated the prognostic significance of pneumonitis and the need for dose reductions due to adverse events. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-81/rc).

Methods

Participants and study design

British Columbia (BC) Cancer is a Canadian provincial organization providing publicly funded oncologic care for the five million residents of BC. There are six BC Cancer centers located across the province. All EGFR mutation testing is conducted centrally at the BC Cancer-Cancer Genetics and Genomic Laboratory. The CGL database was queried to identify all patients with advanced NSCLC (stage IV, 8th edition UICC TNM classification or stage III/recurrent nonresectable disease not amenable to curative intent radiotherapy) harboring any EGFR mutation between 11 March 2020 (date the World Health Organization declared COVID-19 a pandemic) to 31 December 2021. Patients with 19del or L858R mutations who received osimertinib as a first treatment for advanced NSCLC were identified by chart review. Those prescribed osimertinib as second-line (or greater) palliative systemic therapy or as part of a clinical trial were excluded. Data cut-off for inclusion was October 1, 2022.

Chart review was conducted to collect the following information (I) Emergency Room (ER) visit or hospital admission within thirty days prior to the diagnosis of advanced NSCLC; (II) baseline clinical information including age at osimertinib initiation, gender, ECOG performance status, Charlson Comorbidity Index (CCI) score, smoking status, type of EGFR mutation, programmed death ligand 1 (PD-L1) tumor proportion score, stage, presence of brain metastases, and prior curative intent surgery or receipt of adjuvant treatments; (III) date of first and last osimertinib doses and post-progression systemic therapy; (IV) incidence, severity (using Common Terminology Criteria for Adverse Events version 5.0), and treatment of grade ≥2 adverse events attributable to osimertinib. Grade ≥2 toxicity was recorded as these are most clinically relevant; (V) SARS-CoV-2 infection confirmed by reverse transcriptase polymerase chain reaction, rapid antigen test, or serology.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the University of British Columbia Research Ethics Board (protocol No. H22-01350) and individual consent for this retrospective analysis was waived.

Tumor specimen characteristics and assay methods

Using the Maxwell automated system (Promega, Madison, Wisconsin), total nucleic acid was extracted from formalin-fixed paraffin embedded (FFPE) tissue blocks. As per manufacturer's instruction (Illumina, San Diego, California), total nucleic acid was submitted for next generation panel sequencing with the AmpliSeq for Illumina Focus Panel on a MiniSeq sequencer. Primary and secondary data analyses were performed locally at the BC Cancer- Cancer Genetics and Genomics Laboratory using the cloud-based Illumina BaseSpace platform. Deoxyribonucleic acid alterations and potential ribonucleic acid fusion events were flagged by the automated pipeline and then manually evaluated. The Agilent Alissa platform was utilized in order to store, aggregate, and catalog variants in the lab. Further details regarding molecular testing have been previously described (10).

Variables

The primary endpoints were OS and PFS and their correlation with baseline clinico-pathologic characteristics. OS was defined as the time from first osimertinib dose to date of death from any cause. PFS was measured from osimertinib start to date of physician determined progression or death. Patients not experiencing an event of interest were censored at last follow-up.

Secondary endpoints were: (I) the incidence of grade ≥2 adverse events related to osimertinib; (II) a potential association of pneumonitis and need for dose reduction due to toxicity with OS; (III) the incidence and management of COVID-19.

Statistical analysis

Patient and tumor characteristics were reported as the

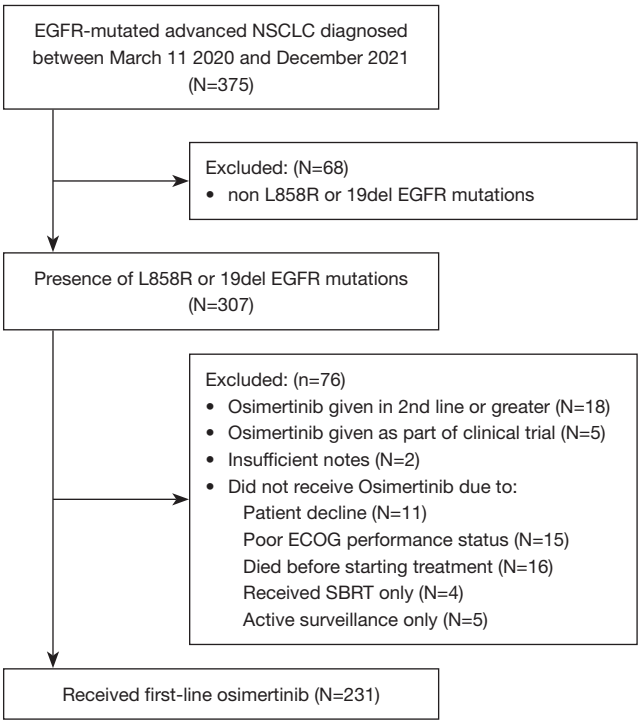

Figure 1 Flowchart of the study. ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; n, patients; NSCLC, non-small cell lung cancer; SBRT, stereotactic body radiation.

median with range of values for continuous variables and frequencies and percentages for categorical variables. Median follow-up time was calculated by the reverse Kaplan-Meier method (11). Survival curves from the date of first osimertinib treatment were generated and groups were compared by the log-rank tests. Univariable and multivariable Cox proportional hazards models were used to examine the association of baseline covariates with OS and PFS. Since grade ≥2 adverse events (i.e., any or pneumonitis) and dose reductions occur after baseline, we included them as time dependent covariates in Cox proportional hazards models to further assess their possible influence on survival. Patients experiencing these were coded as not having them until the time in which they occurred, after which they were coded as having the relevant adverse event or need for dose reduction. Results were summarized as hazard ratios (HR) and 95% confidence intervals (CI). As a second alternative to minimize lead-time bias associated with time-dependent factors, in addition to the time-varying Cox-models above, landmark analysis was used (12). A landmark analysis included patients 'in the risk set' at a set time point, excluding patients who died or were censored before this time point. We used a six-month landmark analysis (from time of osimertinib initiation), which included 210 patients (21 cases excluded: 1 censored and 20 deaths) to compare post-landmark outcomes for patients with a given adverse event grade ≥2 (or need for dose reduction) versus those who did not.

All P values were based on two sided hypotheses tests and those less than 0.05 were considered statistically significant. All analyses were conducted using *R* statistical software version 4.0.3.

Results

Patient population

Two hundred and thirty-one patients with EGFR mutation positive advanced NSCLC were identified (*Figure 1*). For the entire cohort median age was 69.0 years, the majority were female (66.2%), and 105 patients (45.5%) had an ECOG PS ≥2 (*Table 1*). Amongst the 189 patients (81.8%) with *de novo* advanced NSCLC (i.e., initially treated with palliative intent), 58.7% (n=111) presented to the ER within 30 days prior to diagnosis of advanced NSCLC and were either discharged or admitted to hospital; 76.5% of hospital admissions related to urgent therapy for malignancy related complications (i.e., symptomatic pleural effusion or painful bony metastases); 43.9% of individuals (25/57 patients) with brain metastases at diagnosis received treatment with a local modality before starting osimertinib: whole brain radiotherapy alone (n=15), stereotactic radiotherapy alone (n=5), surgical resection only (n=4), and whole brain radiotherapy following by surgical resection (n=1).

Treatment

Osimertinib was administered at the recommended dose of 80 mg PO daily in all except three patients who were prescribed 40 mg PO daily. The median duration of osimertinib therapy was 10.1 months (interquartile range, 5.1–16.5). A proportion of 46.8% of patients were still receiving osimertinib at the time of last follow-up. Second line systemic therapy was delivered in 37 of 110 (33.6%) patients who progressed; post-progression protocols were platinum doublet chemotherapy (n=31), single agent chemotherapy (n=3), first generation EGFR TKI (n=2), and a novel EGFR TKI in a clinical trial (n=1).

Table 1 Baseline characteristics of 231 patients with EGFR-mutated advanced NSCLC receiving first line osimertinib

Characteristics	Value, n (%)
Age (years)	
<65	70 (30.3)
65–74	88 (38.1)
≥75	73 (31.6)
Gender	
Male	78 (33.8)
Female	153 (66.2)
ECOG PS	
0/1	126 (54.5)
2/3	102 (44.2)
4	3 (1.3)
Histology	
Adenocarcinoma	227 (98.3)
Adenosquamous	3 (1.3)
Squamous	1 (0.4)
Charlson Comorbidity Index, median (IQR)	0 (0–1)
Smoking status	
Never smoker	136 (58.9)
Former smoker	83 (35.9)
Current smoker	12 (5.2)
EGFR mutation	
19del	128 (55.4)
L858R	103 (44.6)
PD-L1 staining	
<1%	89 (38.5)
1–49%	66 (28.6)
≥50%	68 (29.4)
Unknown	8 (3.5)
Brain metastases present	57 (24.7)
Initial stage at presentation	
I	20 (8.7)
II	10 (4.3)
IIIA	9 (3.9)
IIIB	6 (2.6)
IIIC	2 (0.8)
IV	184 (79.7)
Advanced NSCLC at presentation	189 (81.8)

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; PD-L1, programmed death ligand 1.

Diagnostic pathway for patients with de novo advanced NSCLC

Tumoral cells were collected from solid tissue or cytology specimens in all patients to determine EGFR mutation status. Twenty-five patients (10.8%) required a repeat biopsy due to insufficient tumoral cell count for molecular testing in the initial specimen. A maximum of two cycles of systemic therapy (i.e., not osimertinib) was prescribed to 14 patients (6.1%) while awaiting EGFR mutation status. The median time from diagnosis of advanced NSCLC to first osimertinib dose (for all 231 patients) was 36.0 days (interquartile range, 26.0–50.0).

Effectiveness

The median follow-up time was 18.7 months (95% CI: 17.4–20.6). At last follow-up, 91 patients (39.4%) had died and no patients were lost to follow-up. Median PFS in the whole cohort was 18.0 months (95% CI: 16.1–26.2) and median OS was 25.4 months (95% CI: 20.3–not reached) (*Figure 2*). Median PFS for individuals with ECOG performance status 0–1, 2–3, or 4 at the start of treatment was 28.3 months (95% CI: 22.3–not reached), 14.5 months (95% CI: 10.8–17.6), and 2.3 months (95% CI: 1.6–not reached), respectively. Similarly, median OS according to baseline ECOG was not reached (95% CI: 25.8 months–not reached), 17.9 months (95% CI: 12.8–25.4), and 3.6 months (95% CI: 1.6–not reached) (*Figure 3*). Baseline clinico-pathologic characteristics were similar amongst patients with ECOG performance status 0–1 *vs.* 2–4, aside from brain metastases being more common in the latter group (Table S1).

Characteristics associated with shorter PFS on multivariable Cox regression analysis were age ≥75 years (*vs.* <75 years; HR: 1.89, 95% CI: 1.25–2.78, P=0.0021), L858R mutation (*vs.* 19del; HR: 1.43, 95% CI: 1.00–2.06, P=0.050), ECOG performance status 2–3 (*vs.* 0-1; HR: 2.45, 95% CI: 1.72–3.49, P<0.001), ECOG performance status 4 (*vs.* 0–1; HR: 22.27, 95% CI: 6.35–78.10, P<0.001), PD-L1 tumor proportion score ≥50% (*vs.* <1%; HR: 1.59, 95% CI: 1.07–2.36, P=0.023), and current smokers (*vs.* never smokers; HR: 5.21, 95% CI: 2.90–9.36, P<0.001) (*Table 2*).

On multivariable Cox regression analysis for OS, baseline factors associated with a higher risk of death were ECOG performance status 2–3 (*vs.* 0–1; HR: 2.46, 95% CI: 1.55–3.88, P<0.001), ECOG performance status 4 (*vs.* 0/1; HR: 30.77, 95% CI: 8.51–111.34, P<0.001), PD-L1

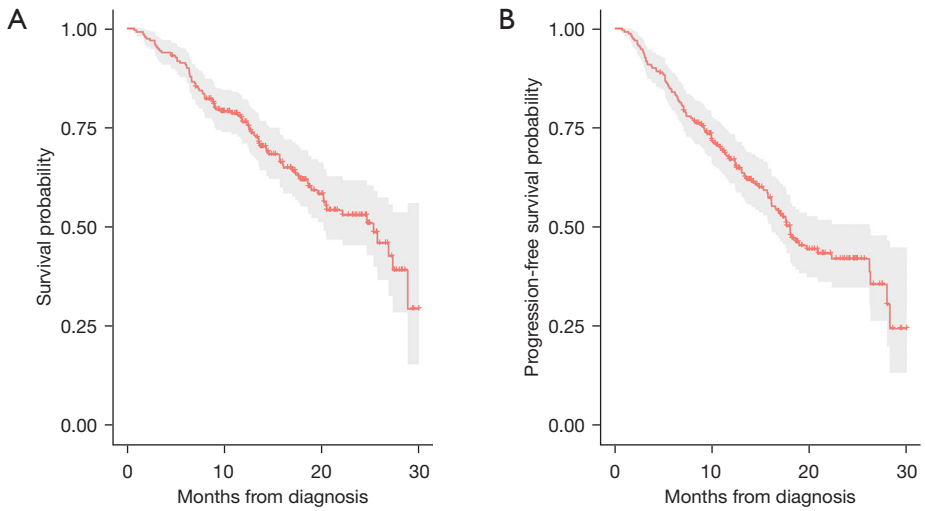

Figure 2 Kaplan-Meier curves of overall survival (A) and progression free survival (B) for all 231 patients. OS, overall survival; PFS, progression free survival.

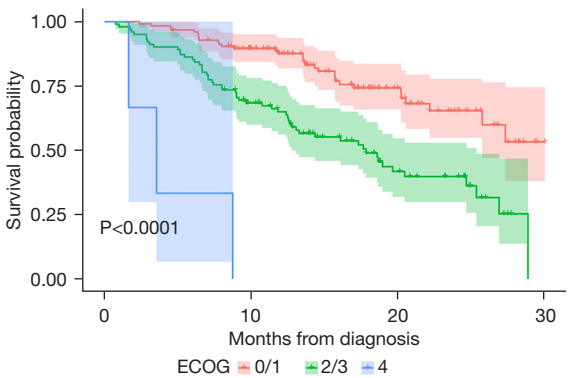

Figure 3 Kaplan-Meier curves of overall survival for patients with baseline ECOG performance status 0/1 (126 patients), 2/3 (102 patients), and 4 (3 patients). ECOG, Eastern Cooperative Oncology Group.

tumor proportion score ≥50% (*vs.* <1%; HR: 1.82, 95% CI: 1.10–2.99, P=0.019), current smokers (*vs.* never smokers; HR: 2.91, 95% CI: 1.31–6.50, P=0.0090), and the presence of brain metastases (*vs.* none; HR: 1.68, 95% CI: 1.04–2.71, P=0.035) (*Table 3*).

Safety

During all follow-up, 123 patients (53.2%) experienced grade ≥2 adverse events while 38 patients (16.5%) developed grade ≥3 adverse events (*Table 4*). The most commonly observed toxicities were dermatitis including acneiform rash and dry skin (16.0%) and diarrhea (12.1%). 3.9% of the cohort (9 patients) developed pneumonitis with 1 case being fatal. Osimertinib was discontinued due to toxicity in 15 patients (6.5%): pneumonitis (n=7), diarrhea (n=2), fatigue (n=2), pancytopenia (n=2), dermatitis (n=1), cardiomyopathy (n=1). Nine-point-one percent (n=21) of patients needed a treatment delay while 10.8% (25 patients) required a dose reduction due to drug toxicity. No difference in OS was observed amongst individuals requiring a dose reduction (compared to full dose osimertinib) using six-month landmark analysis (median OS: not reached *vs.* 19.8 months; P=0.92). These findings were confirmed using univariable time dependent Cox regression (HR: 0.89, 95% CI: 0.36–2.20; P=0.80).

Association of pneumonitis with OS

Six-month landmark analysis for pneumonitis was not possible as there were only 5 cases by that timepoint. On univariable time dependent Cox regression analysis involving 9 cases, development of pneumonitis (*vs.* absence of pneumonitis) was weakly associated with worse OS (HR: 2.59, 95% CI: 0.94–7.12, P=0.066).

COVID-19

Ten-point-eight percent (n=25) of the cohort were diagnosed with SARS-CoV-2 infection. Osimertinib was temporarily held due to concurrent COVID-19 in 3 patients. COVID-19

Table 2 Univariable and multivariable time dependent Cox regression analysis of progression free survival for 231 patients with EGFR-mutated advanced NSCLC treated with first-line osimertinib

Variables	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Age (≥75 *vs.* <75 years)	1.37 (0.93–2.00)	0.11	1.89 (1.25–2.78)	0.0021
Gender (male *vs.* female)	1.06 (0.72–1.56)	0.77	1.17 (0.82–1.69)	0.39
ECOG performance status				
2/3 *vs.* 0/1	2.53 (1.72–3.72)	<0.001	2.45 (1.72–3.49)	<0.001
4 *vs.* 0/1	15.56 (4.72–51.31)	<0.001	22.27 (6.35–78.10)	<0.001
CCI (per 1 unit increase)	0.95 (0.80–1.13)	0.57	0.84 (0.71–1.00)	0.056
Smoking status				
Former *vs.* never	1.44 (0.97–2.15)	0.070	1.01(0.69–1.48)	0.95
Current *vs.* never	4.77 (2.47–9.20)	<0.001	5.21 (2.90–9.36)	<0.001
Present with advanced NSCLC (yes *vs.* no)	1.23 (0.74–2.07)	0.42	0.85 (0.52–1.41)	0.53
Brain metastases at baseline (present *vs.* none)	1.37 (0.91–2.06)	0.13	1.29 (0.87–1.92)	0.21
EGFR mutation (L858R *vs.* 19del)	1.57 (1.08–2.27)	0.017	1.43 (1.00–2.06)	0.050
PD-L1 tumor proportion score				
≥50% *vs.* <1%	1.74 (1.13–2.68)	0.012	1.59 (1.07–2.36)	0.023
1–49% *vs.* <1%	0.96 (0.59–1.55)	0.85	1.16 (0.75–1.80)	0.50
Unknown *vs.* <1%	0.99 (0.31–3.21)	0.99	0.99 (0.30–3.23)	0.99
Adverse event ≥ grade 2 (present *vs.* none)	1.20 (0.81–1.76)	0.36	0.79 (0.53–1.17)	0.24

CCI, Charlson Comorbidity Index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1.

directed therapy was prescribed to 4 individuals (paxlovid n=2, sotrovimab n=2). Ultimately 4 patients (1.7%) were hospitalized due to severe sequelae from SARS-CoV-2 infection and 1 patient (0.4%) died.

Discussion

In this large multicenter retrospective study, we evaluated the real world efficacy and safety of first-line osimertinib in patients with EGFR-mutated advanced NSCLC during the COVID-19 pandemic. Clinical (age, ECOG performance status, and smoking history) and pathologic (PD-L1 expression and mutation type) characteristics associated with PFS were identified. While the median PFS in the cohort was similar to that observed in the FLAURA study, median OS was lower likely attributable to a high proportion of patients with poor ECOG performance status and modest use of post-osimertinib systemic therapy. Importantly, osimertinib was well tolerated with a low incidence of severe drug related toxicity. While the development of pneumonitis was a negative prognostic factor, only 4% of the cohort experienced this adverse event.

Three of every five patients with *de novo* advanced NSCLC in this study were seen in the Emergency Room (and either discharged or admitted to hospital) within 30 days prior to being diagnosed with lung cancer. Approximately 77% of hospital admissions were required for urgent medical interventions due to malignancy-related complications in individuals not previously known to have cancer. Diagnosis of cancer as an emergency presentation is an established negative prognostic factor (13). Prior studies in Canada and the United Kingdom have estimated that between 36–39% of lung cancer cases are initially discovered after ER visits (14,15). Disruptions in upstream healthcare services could explain the high proportion of patients diagnosed with advanced NSCLC after presenting

Table 3 Univariable and multivariable time dependent Cox regression analysis of overall survival for 231 patients with EGFR-mutated advanced NSCLC treated with first-line osimertinib

Variables	Univariable		Multivariable	
	HR (95% CI)	P	HR (95% CI)	P
Age (≥75 *vs.* <75 years)	1.45 (0.94–2.22)	0.087	1.42 (0.86–2.38)	0.16
Gender (male *vs.* female)	1.03 (0.67–1.58)	0.91	1.13 (0.71–1.81)	0.60
ECOG performance status				
2/3 *vs.* 0/1	2.66 (1.72–4.12)	<0.001	2.46 (1.55–3.88)	<0.001
4 *vs.* 0/1	20.01 (5.94– 67.39)	<0.001	30.77 (8.51–111.34)	<0.001
CCI (per 1 unit increase)	1.03 (0.86–1.23)	0.75	0.91 (0.74–1.13)	0.39
Smoking status				
Former *vs.* never	1.60 (1.04–2.48)	0.034	1.31 (0.81–2.12)	0.26
Current *vs.* never	3.23 (1.51–6.90)	0.002	2.91 (1.31–6.50)	0.0090
Present with advanced NSCLC (yes *vs.* no)	1.21 (0.67–2.17)	0.53	0.97 (0.50–1.89)	0.92
Brain metastases at baseline (present *vs.* none)	1.57 (1.00–2.45)	0.048	1.68 (1.04–2.71)	0.035
EGFR mutation (L858R *vs.* 19del)	1.61 (1.06–2.43)	0.025	1.26 (0.80–1.99)	0.32
PD-L1 tumor proportion score				
≥50% *vs.* <1%	1.71 (1.06–2.76)	0.027	1.82 (1.10–2.99)	0.019
1–49% *vs.* <1%	0.92 (0.53–1.59)	0.76	1.14 (0.64–2.01)	0.66
Unknown *vs.* <1%	0.91 (0.22–3.82)	0.90	1.28 (0.30–5.48)	0.74
Adverse event ≥ grade 2 (present *vs.* none)	1.09 (0.73–1.63)	0.70	1.26 (0.78–2.02)	0.34

CCI, Charlson Comorbidity Index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand 1.

to the ER. During the first year of the COVID-19 pandemic, Canadians were less likely to access primary care services and many General Practitioners reduced their work hours (16,17). Concurrently, non-emergent cancer screenings and diagnostic tests were postponed in order to conserve hospital capacity in preparation for a presumed surge in SARS-CoV-2 infected patients.

The median PFS of 18.0 months noted in the current study is similar to that reported in the phase III FLAURA trial and two other real world studies (3,18,19). A retrospective series of front-line osimertinib by Sakata *et al.* based in Japan with 538 patients reported a median PFS of 20.5 months (18). Moreover, a prospective observational study of osimertinib in Italy including 126 participants, observed a median PFS of 18.9 months (19). Nevertheless, the median OS in the current series was approximately thirteen months shorter than in the FLAURA trial and this likely relates to the prevalence of patients with poor ECOG performance status and lower usage of post-progression systemic therapy. Specifically, only 34% of patients received an additional line of treatment after progression on osimertinib. It is conceivable that as nearly half of the cohort had an ECOG performance status ≥2 at baseline, many were judged too ill to tolerate standard second line therapy with doublet cytotoxic chemotherapy.

While the FLAURA study used 65 years as a threshold to define older age, the incidence of lung cancer in Canada is greatest amongst those aged 75 to 84 years (20). In the current study, 32% of the cohort were ≥75 years at the initiation of osimertinib and older age (*vs.* <75 years) was associated with shorter PFS on multivariable analysis. Safe delivery of EGFR tyrosine kinase inhibitor therapy in the elderly is complicated by concerns regarding polypharmacy, multiple chronic conditions, and heterogeneity in functional status; moreover, increasing age is also a risk factor for drug-induced pneumonitis (21). Conflicting data exist regarding

Table 4 Adverse events ≥ grade 2 attributed to osimertinib during all follow-up

Adverse event	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)
Any	85 (36.8)	35 (15.2)	2 (0.9)	1 (0.4)
Alopecia	1 (0.4)	0	0	0
Arthralgias	2 (0.9)	0	0	0
Cardiomyopathy	0	1 (0.4)	0	0
Diarrhea	22 (9.5)	6 (2.6)	0	0
Dermatitis	29 (12.6)	8 (3.5)	0	0
Fatigue	1 (0.4)	4 (1.7)	0	0
Hand and Foot Syndrome	1 (0.4)	0	0	0
Hepatitis	0	3 (1.3)	0	0
Increased creatinine	1 (0.4)	0	0	0
Mucositis	7 (3.0)	2 (0.9)	0	0
Nausea	4 (1.7)	1 (0.4)	0	0
Pancytopenia	1 (0.4)	1 (0.4)	0	0
Paronychia	13 (5.6)	3 (1.3)	0	0
Pericardial effusion	1 (0.4)	0	0	0
Peripheral edema	1 (0.4)	0	0	0
Pneumonitis	1 (0.4)	5 (2.2)	2 (0.9)	1 (0.4)
Thrombocytopenia	0	1 (0.4)	0	0

n, number of patients with adverse event; %, number of patients who developed adverse event/231

the prognostic significance of advanced age amongst patients receiving osimertinib. The phase II SPIRAL-0 trial examined the efficacy of osimertinib as a first-line treatment for patients aged ≥75 years with EGFR-mutated advanced NSCLC (21). A total of 38 participants were enrolled and the 1-year PFS rate of 59% (95% CI: 46–73%) did not meet the primary endpoint based on the lower bound of the confidence interval crossing 50%. In contrast, a prospective observational study by Igawa *et al.* with similar inclusion criteria found the median PFS amongst 43 participants to be comparable to those observed in the FLAURA study (22). Given the increased prevalence of NSCLC with age, larger prospective studies would be helpful to clarify the benefits and risks of first-line osimertinib in older patients and to facilitate informed consent.

Several studies have examined the impact of smoking status on response to first generation EGFR TKI. A meta-analysis conducted by Zhang *et al.* demonstrated superior PFS in never smokers treated with first generation EGFR TKI compared to former or current smokers (23). Furthermore, a retrospective series conducted in Korea noted reduced PFS amongst heavier smokers (≥30 pack-year) versus never smokers or those with <30 pack-year smoking history (24). On multivariable analysis, we found OS to be longer in never smokers compared to current smokers. Differences in outcomes based on smoking status might be attributable to multiple factors. For example, the average number of point mutations in NSCLC from smokers is significantly higher than in lung tumors from never smokers (25); as such there could be several oncogenic drivers (in addition to EGFR) in patients with a history of cigarette smoke exposure.

In the present study, a PD-L1 tumor proportion score ≥50% (*vs.* <1%) was associated with shorter PFS and OS. In a subset analysis of the FLAURA study, median PFS with osimertinib was similar in patients with PD-L1 positive (tumor cell staining ≥1% using the SP263 immunohistochemical assay) and PD-L1 negative tumors (26). We chose a threshold PD-L1 expression of 50% (using the 22C3 pharmDx assay) as a tumor proportion score equal to or greater than this value predicts response

to pembrolizumab (a programmed death-1 inhibitor) monotherapy (27). Our findings are consistent with those of Sakata *et al.* who found high tumoral PD-L1 expression to be associated with reduced osimertinib efficacy (18). Mechanisms underlying resistance to osimertinib relating to the PD-L1 signalling pathway are incompletely understood at this time but could involve upregulated expression of Bcl-2 associated athanogene-1 (BAG-1) and yes associated protein 1 (YAP1) (28,29).

In general, osimertinib was well tolerated in the studied cohort. For example, the incidence of drug-related ≥ grade 3 adverse events (17% *vs.* 34%), need for treatment delay (9% *vs.* 25%), and osimertinib discontinuation resulting from toxicity (7% *vs.* 13%) were lower than in FLAURA. Dose reductions prompted by adverse events were not associated with shorter OS. These results could provide reassurance to patients concerned about compromised efficacy outcomes if a lower dose is recommended. Drug-related pneumonitis is a potentially life-threatening complication of EGFR TKI therapy. In the current series, 4% (n=9) of patients developed pneumonitis and 1 case was fatal. Using time dependent Cox regression analysis, we calculated a 2.6-fold increase in risk of death amongst individuals who experienced pneumonitis from osimertinib compared to those who did not. Similarly, Sato *et al.* found PFS was shorter in patients developing pneumonitis (*vs.* none) from osimertinib within three months of drug initiation (30).

This study has several limitations, including patient and treatment selection biases inherent in retrospective studies. Only patients with 19del or L858R mutations were included, as such the results might differ for individuals with uncommon EGFR mutations. Identification of a timepoint for landmark analysis is an attempt to capture as many toxicity events as possible with the least number of progression events. Since selection of a landmark is somewhat arbitrary, we also utilized time dependent Cox regression analysis (12).

Lastly, another limitation is that COVID-19 vaccination status was not routinely collected in charts. However, we note that despite multiple contacts with the healthcare system, the proportion of patients diagnosed with COVID-19 in this study (10.8%) was similar to the cumulative incidence of COVID-19 in the province of British Columbia (7.5%) during the same time period (31). Importantly, only four patients were hospitalized because of SARS-CoV-2 infection and one died (0.4%) as a direct result. Beginning in the first wave of COVID-19, BC Cancer aggressively implemented strategies aimed at limiting viral transmission amongst patients and healthcare workers. Components of this policy included a shift to virtual consultations, use of personal protective equipment, screening patients for symptoms of COVID-19, and prioritizing patients on anti-cancer therapy for vaccinations when they became available. As such, EGFR TKI therapy can be given safely while adhering to COVID-19 risk mitigation strategies.

Conclusions

In the current study conducted during the COVID-19 pandemic, many patients presented to the Emergency Room with *de novo* EGFR-mutated advanced NSCLC. Nearly half of the cohort had a poor ECOG performance status at treatment initiation which likely accounted for a median OS lower than in the FLAURA trial. We identified demographic and pathologic characteristics associated with PFS and OS that can assist in risk stratification. Reassuringly, the incidence of severe adverse effects was low and dose reductions for side-effects did not appear to compromise survival. Efforts to minimize delays in the diagnosis of EGFR-mutated advanced NSCLC are needed so that life prolonging treatments can be initiated as early as possible.

Acknowledgments

Funding: This work was supported by a grant from the BC Cancer Foundation (Grant No. F22-05558 to DK).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-81/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-81/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-81/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-81/coif). PTT receives writing and royalty fees from UpToDate, Wolters Kluwer Health Publishing. SY has received consulting fees from Amgen, AstraZeneca, Bayer, Incyte, and Roche. DK has

received a grant from the BC Cancer Foundation (Grant No. F22-05558) to support this manuscript and has received unrestricted educational grants from AstraZeneca and speaker honoraria from Merck and Bristol-Myers Squibb. 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 the University of British Columbia Research Ethics Board (protocol No. H22-01350) and individual consent for this retrospective analysis was waived.

References

1. Dearden S, Stevens J, Wu YL, et al. Mutation incidence and coincidence in non small-cell lung cancer: meta-analyses by ethnicity and histology (mutMap). Ann Oncol 2013;24:2371-6.
2. Lee CK, Davies L, Wu YL, et al. Gefitinib or Erlotinib vs Chemotherapy for EGFR Mutation-Positive Lung Cancer: Individual Patient Data Meta-Analysis of Overall Survival. J Natl Cancer Inst 2017;109.
3. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382:41-50.
4. Lilenbaum RC, Cashy J, Hensing TA, et al. Prevalence of poor performance status in lung cancer patients: implications for research. J Thorac Oncol 2008;3:125-9.
5. Radzikowska E, Głaz P, Roszkowski K. Lung cancer in women: age, smoking, histology, performance status, stage, initial treatment and survival. Population-based study of 20 561 cases. Ann Oncol 2002;13:1087-93.
6. Inoue A, Kobayashi K, Usui K, et al; North East Japan Gefitinib Study Group. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol 2009;27:1394-400. Erratum in: J Clin Oncol 2009;27:3071.
7. Igawa S, Fukui T, Kasajima M, et al. First-line osimertinib for poor performance status patients with EGFR mutation-positive non-small cell lung cancer: A prospective observational study. Invest New Drugs 2022;40:430-7.
8. Singh AP, Berman AT, Marmarelis ME, et al. Management of Lung Cancer During the COVID-19 Pandemic. JCO Oncol Pract 2020;16:579-86.
9. Garassino MC, Whisenant JG, Huang LC, et al. COVID-19 in patients with thoracic malignancies (TERAVOLT): first results of an international, registry-based, cohort study. Lancet Oncol 2020;21:914-22.
10. Wong SK, Alex D, Bosdet D, et al. MET exon 14 skipping mutation positive non-small cell lung cancer: Response to systemic therapy. Lung Cancer 2021;154:142-5.
11. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. Control Clin Trials 1996;17:343-6.
12. Kfoury M, Najean M, Lappara A, et al. Analysis of the association between prospectively collected immune-related adverse events and survival in patients with solid tumor treated with immune-checkpoint blockers, taking into account immortal-time bias. Cancer Treat Rev 2022;110:102452.
13. McPhail S, Swann R, Johnson SA, et al. Risk factors and prognostic implications of diagnosis of cancer within 30 days after an emergency hospital admission (emergency presentation): an International Cancer Benchmarking Partnership (ICBP) population-based study. Lancet Oncol 2022;23:587-600.
14. Suhail A, Crocker CE, Das B, et al. Initial presentation of lung cancer in the emergency department: a descriptive analysis. CMAJ Open 2019;7:E117-23.
15. Elliss-Brookes L, McPhail S, Ives A, et al. Routes to diagnosis for cancer - determining the patient journey using multiple routine data sets. Br J Cancer 2012;107:1220-6.
16. Huston P, Campbell J, Russell G, et al. COVID-19 and primary care in six countries. BJGP Open 2020;4:bjgpopen20X101128.
17. The College of Family Physicians of Canada. Family Physician's Response to the COVID-19 Pandemic 2022. (cited 2023 January 14). Available online: https://www.cfpc.ca/CFPC/media/Resources/Research/Covid-19-Member-Survey-ENG-Final.pdf.

18. Sakata Y, Sakata S, Oya Y, et al. Osimertinib as first-line treatment for advanced epidermal growth factor receptor mutation-positive non-small-cell lung cancer in a real-world setting (OSI-FACT). Eur J Cancer 2021;159:144-53.
19. Lorenzi M, Ferro A, Cecere F, et al. First-Line Osimertinib in Patients with EGFR-Mutant Advanced Non-Small Cell Lung Cancer: Outcome and Safety in the Real World: FLOWER Study. Oncologist 2022;27:87-e115.
20. Government of Canada. Canadian Cancer Statistics, 2020. (cited 2022 December 2). Available online: https://www150.statcan.gc.ca/n1/daily-quotidien/200922/dq200922b-eng.htm.
21. Chihara Y, Takeda T, Goto Y, et al. A Phase II Trial on Osimertinib as a First-Line Treatment for EGFR Mutation-Positive Advanced NSCLC in Elderly Patients: The SPIRAL-0 Study. Oncologist 2022;27:903-e834.
22. Igawa S, Kasajima M, Ono T, et al. A Prospective Observational Study of Osimertinib for Chemo-Naive Elderly Patients with EGFR Mutation-Positive Non-Small Cell Lung Cancer. Cancer Manag Res 2021;13:8695-705.
23. Zhang Y, Kang S, Fang W, et al. Impact of smoking status on EGFR-TKI efficacy for advanced non-small-cell lung cancer in EGFR mutants: a meta-analysis. Clin Lung Cancer 2015;16:144-151.e1.
24. Kim MH, Kim HR, Cho BC, et al. Impact of cigarette smoking on response to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors in lung adenocarcinoma with activating EGFR mutations. Lung Cancer 2014;84:196-202.
25. Govindan R, Ding L, Griffith M, et al. Genomic landscape of non-small cell lung cancer in smokers and never-smokers. Cell 2012;150:1121-34.
26. Brown H, Vansteenkiste J, Nakagawa K, et al. Programmed Cell Death Ligand 1 Expression in Untreated EGFR Mutated Advanced NSCLC and Response to Osimertinib Versus Comparator in FLAURA. J Thorac Oncol 2020;15:138-43.
27. Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med 2016;375:1823-33.
28. Lin PL, Wu TC, Wu DW, et al. An increase in BAG-1 by PD-L1 confers resistance to tyrosine kinase inhibitor in non-small cell lung cancer via persistent activation of ERK signalling. Eur J Cancer 2017;85:95-105.
29. Tung JN, Lin PL, Wang YC, et al. PD-L1 confers resistance to EGFR mutation-independent tyrosine kinase inhibitors in non-small cell lung cancer via upregulation of YAP1 expression. Oncotarget 2017;9:4637-46.
30. Sato Y, Sumikawa H, Shibaki R, et al. Drug-Related Pneumonitis Induced by Osimertinib as First-Line Treatment for Epidermal Growth Factor Receptor Mutation-Positive Non-Small Cell Lung Cancer: A Real-World Setting. Chest 2022;162:1188-98.
31. BC Center For Disease Control. Weekly Reporting of COVID-19 Cases 2022. (cited 2023 January 14). Available online: http://www.bccdc.ca/Health-Info-Site/Documents/COVID-19_Weekly_Report/COVID_weekly_report_09292022.pdf.

Cite this article as: Lakkunarajah S, Truong PT, Bone JN, Hughesman C, Yip S, Alex D, Hart J, Pollock P, Egli S, Clarkson M, Lesperance M, Ksienski D. First-line osimertinib for patients with EGFR-mutated advanced non-small cell lung cancer: efficacy and safety during the COVID-19 pandemic. Transl Lung Cancer Res 2023;12(7):1454-1465. doi: 10.21037/tlcr-23-81