Osimertinib in NSCLC: Real-World Data From New Zealand

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ABSTRACT

Introduction: EGFR tyrosine kinase inhibitors (TKIs) are more effective than chemotherapy in patients with EGFR-mutant NSCLC. Disease progression on EGFR TKI therapy occurs most often owing to acquired resistance from the gain of an EGFR T790M mutation. Osimertinib, a third-generation EGFR TKI, significantly improves outcomes in patients with EGFR T790M mutation–positive NSCLC compared with platinum–pemetrexed chemotherapy. We retrospectively reviewed clinical outcomes for patients receiving osimertinib through a compassionate access program in New Zealand.

Methods: Patients with a biopsy-proven or plasma-circulating tumor-DNA–proven EGFR T790M mutation received osimertinib. Data on patient and tumor characteristics, treatments, and outcomes were collected retrospectively. Survival outcomes were calculated from the time of osimertinib commencement.

Results: A total of 39 patients were enrolled, and data from 37 patients were analyzed. EGFR T790M status was found from plasma samples in six of 37 (16%) patients. A total of 27 of 37 patients (73%) used osimertinib as a second-line treatment. At the time of data analysis, median follow-up was 18.8 months (range 1.5–29). Overall response rate was 70% (95% confidence interval [CI]: 53–84) (26 of 37). Progression-free survival (PFS) at 12 months was 62% (95% CI: 44.8–77.5), and median PFS was 14.6 months (95% CI: 12.4–16.8). Median overall survival was not reached. Osimertinib was well tolerated, with grade 1 gastrointestinal and skin toxicity as the most common adverse effects. Three patients required dose adjustments or cessation owing to toxicity.

Conclusion: Osimertinib is an effective treatment for New Zealanders with EGFR T790M mutated NSCLC who have progressed after first or subsequent lines of therapy.

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Keywords: Non–small cell lung cancer; T790M mutation; Epidermal growth factor receptor; Tyrosine kinase inhibitor; New Zealand; Osimertinib

Introduction

Lung cancer is the leading cause of cancer-related mortality internationally and in New Zealand.1 NSCLC accounts for approximately 80% of lung cancer. A subgroup of nonsquamous NSCLC harbors a driver mutation in the tyrosine kinase domain of the EGFR gene. EGFR tyrosine kinase inhibitors (TKIs) are accepted as the international standard first-line treatment for advanced EGFR-mutant NSCLC in preference to chemotherapy.2 First-generation EGFR TKIs, such as erlotinib and gefitinib, have improved progression-free survival (PFS) compared with platinum-based doublet chemotherapy.
as reported in multiple phase III clinical trials.\textsuperscript{3-6} Inevitably, all patients who receive first-line EGFR TKI therapy will progress because of acquired resistance, of which approximately 60% is due to acquisition of the $EGFR$ T790M mutation.\textsuperscript{7-9} Osimertinib, a third-generation EGFR TKI, significantly improves PFS in patients with $EGFR$ T790M mutation–positive NSCLC compared with that of platinum–pemetrexed chemotherapy in the second-line setting.\textsuperscript{10,11} Recently, PFS benefit was also reported for osimertinib in the first-line setting, including for patients who harbored exon 19 deletion and L858R mutations without the $EGFR$ T790M mutation.\textsuperscript{12}

For patients with advanced $EGFR$-mutant NSCLC in New Zealand, erlotinib and gefitinib are funded as first-line treatment, but there are no funded second-line TKI options. Cytotoxic chemotherapy remains the only publicly funded second-line option. Before its regulatory approval in New Zealand, osimertinib was available through a compassionate access program for patients in New Zealand. We aim to assess the efficacy and tolerability of osimertinib in our local Auckland regional population. We have undertaken a retrospective review of clinical records from the local compassionate access program.

Materials and Methods

From September 2015 until May 2018, patients in New Zealand with $EGFR$-mutant NSCLC who had progressed on a first-line TKI and had a proven $EGFR$ T790M mutation were able to obtain osimertinib through a compassionate access scheme. Enrolment was through an online application process to AstraZeneca. Patient participation in the access program was voluntary and without incentive or reimbursement. Eligibility criteria for the compassionate access program included normal corrected QT (QTc) interval on electrocardiogram and acceptable baseline blood results.

Osimertinib was prescribed at the Auckland Regional Cancer and Blood Service, Auckland City Hospital, or an Auckland private medical oncology center. Patients gave their consent under Section 29 of the New Zealand Medicines Act (1981) until osimertinib was MEDSAFE registered in October 2017.\textsuperscript{13} All the authors were part of the clinical team that cared for participating patients with lung cancer and included physicians and an oncology nurse practitioner. All members of the team had access to electronic clinical records of patients who received osimertinib through the access program. The patients were reviewed every 3 months in an outpatient setting. Regular restaging computed tomography scans were used to monitor disease response in accordance with local clinical practice. The treatment was allowed to be continued for patients with radiological progression who gained clinical benefit as assessed by a local physician. Radiological disease assessment was reported as progression, stable disease, or with response, but Response Evaluation Criteria in Solid Tumors (RECIST) criteria were not applied. We did not attempt to retrospectively apply the RECIST criteria through repeat tumor assessment.

After ethics approval by the Auckland District Health Board internal process (International Electrotechnical Commission approval number A+7912), we retrospectively reviewed the electronic clinical records of patients in the access program.

Patients who commenced osimertinib between October 2015 and November 2017, were included for analysis. These patients were also required to have electronic medical records available and have received a minimum of 6 weeks of osimertinib treatment with at least one on-treatment computed tomography staging scan available for disease assessment. We collected data on patient demographics, pathologic diagnosis, previous treatments, method and timing of $EGFR$ T790M testing, disease response, progression and survival on osimertinib, and adverse events. We did not collect data from patients who had progression on first-line EGFR TKI therapy but did not report $EGFR$ T790M mutation; hence, we were unable to calculate the local prevalence of $EGFR$ T790M-mediated resistance.

Adverse events (frequency and grade), dose changes, and discontinuation rates were noted from clinical records and were summarized descriptively. Patient-reported outcome or quality of life data were not available.

Statistical Analysis

Baseline patient demographics, cancer type, mutations, stage, and all cancer treatments since diagnosis are summarized descriptively. We calculated overall response rate (ORR) and survival measures. Survival estimates were calculated using the Kaplan-Meier method. PFS was calculated from the date of osimertinib commencement to the date of first radiological progression or death. Time-to-treatment discontinuation (TTD) was calculated from the date of osimertinib commencement to the date of osimertinib discontinuation. Date of osimertinib discontinuation was defined as the date osimertinib was documented to cease or the date of last clinical contact or death for patients who continued on osimertinib. Overall survival (OS) was calculated from the date of osimertinib commencement to the date of death. For patients who had not reached those end points at the time of the analysis, PFS and OS were censored based on the date they were last known not to have progressed or were still alive, respectively.
Exact 95% binomial confidence intervals (95% CIs) were calculated for response rates.

Analyses were performed using SPSS version 24.0.0.0 (IBM Corporation, Armonk, NY).

Results
A total of 39 patients were enrolled in the access program. Two patients were excluded from this analysis owing to death before receiving osimertinib (n = 1) or loss to follow-up (n = 1). We analyzed data from 37 patients.

Baseline Characteristics
The median age of patients in the access program was 64.2 years (range, 43.4–85.2). A total of 68% of patients were female, and 76% had never smoked. The study cohort included Asian (45%), New Zealand–European (34%), Pacific Islander (16%), and Indian (5%) ethnicities, but no Māori patient received osimertinib. The most common histologic diagnosis was adenocarcinoma (97%), and the most common type of original EGFR-activating mutation was an exon 19 deletion in 24 patients (65%) followed by L858R in seven patients (19%), de novo EGFR T790M in four patients (11%), and S7681 in one patient (3%). Table 1 shows the baseline characteristics of the patients in the access program.

A total of 10 patients (27%) had central nervous system disease at the start of osimertinib treatment. Eight patients (80%) had brain radiation before osimertinib treatment, and only one patient required further brain radiation during treatment with osimertinib. Two patients with known central nervous system disease died within 10 weeks of commencing osimertinib.

A total of 27 patients (73%) received osimertinib as second-line treatment. Six patients (16%) received osimertinib as third-line treatment, and three patients (8%) received osimertinib as fourth-line treatment. Previous treatments included first-generation TKIs (n = 36), cytotoxic chemotherapy (n = 8), and second-generation TKI therapy (n = 2) (Table 1).

T790M Mutation Detection
Diagnosis of EGFR T790M mutation was made from biopsy tissue (81%), plasma testing (16%), or pleural aspirate (3%) (Table 2). Median time from disease progression to EGFR T790M mutation detection was 1.25 months (range 0–12 mo). Two patients had an extended time between detection and treatment. One patient had de novo EGFR T790M mutation that responded to first-generation TKI, and the other patient had further cytotoxic treatment. Seven patients required more than one test before detection of EGFR T790M mutation owing to insufficient sample quality (Table 2).

Efficacy
Median follow-up time for patients in the program was 16 months (range, 1.5–27). At the time of the analysis on September 30, 2018, 22 patients (60%) had progressed and 11 patients (30%) had died. ORR was 70% (95% CI: 53–84). Median PFS was 14.6 months (95% CI: 12.4–16.8) (Fig. 1), and PFS at 12 months was 62% (95% CI: 44.8–77.5) (Table 3). The median TTD was 21.9 months (95% CI: 12.5–31.2) reflecting that

| Table 1. Baseline Characteristics |
|----------------------------------|
| **Baseline Characteristic**      | **Patients N = 37** |
| Median age, y (range)            | 64.2 (43.4–85.2)  |
| Female, n (%)                    | 25 (68%)          |
| **Ethnicity**                    |                   |
| SE Asian                         | 16 (43%)          |
| NZ European                      | 13 (35%)          |
| Pacific Islander                 | 6 (16%)           |
| Indian                           | 2 (5%)            |
| NZ Māori                         | 0 (0%)            |
| **Smoking status, n (%)**        |                   |
| Nonsmoker                        | 28 (76%)          |
| Ex-smoker                        | 8 (20%)           |
| Current-smoker                   | 1 (3%)            |
| **Disease characteristics**      |                   |
| CNS disease                      | 10 (27%)          |
| Stage III                        | 5 (13%)           |
| Stage IV                         | 32 (86%)          |
| **Histology**                    |                   |
| Adenocarcinoma                   | 36 (97%)          |
| Adenosquamous                    | 1 (3%)            |
| **EGFR mutation**                |                   |
| Exon 19 del                      | 24 (65%)          |
| L858R                            | 8 (22%)           |
| S7681                            | 1 (3%)            |
| De novo T790M                    | 4 (11%)           |
| Dual mutations                   | 4 (11%)           |
| **Number of previous treatments**|                   |
| 0                                | 1 (3%)            |
| 1                                | 27 (73%)          |
| 2                                | 6 (16%)           |
| 3+                               | 3 (8%)            |
| **Type of previous treatments**  |                   |
| First-generation TKIs            | 36 (97%)          |
| Second-generation TKIs           | 2 (5%)            |
| Chemotherapy                     | 8 (21%)           |

NZ, New Zealand; CNS, central nervous system; SE, southeast; TKI, tyrosine kinase inhibitor.
some patients received treatment beyond radiological progression (Fig. 2). Data were immature for OS analysis with the median not reached at time of analysis.

**Patients With De Novo EGFR T790M Mutation**

All four cases of de novo EGFR T790M mutation were found in patients with dual activating EGFR mutations (Table 1). One patient received osimertinib as first-line treatment, and three patients received osimertinib as second-line treatment. Patients with de novo EGFR T790M mutation seemed to have shorter PFS with first-generation TKI therapy with two of the three patients progressing within a month of starting a first-generation TKI. Patients with de novo EGFR T790M mutation had PFS of 10.3 months, 10.8 months, and 22.9 months on osimertinib as second-line treatment and 6.6 months on osimertinib as first-line treatment.

**Disease Progression**

Of the 26 patients with progressive disease, 14 continued osimertinib beyond first radiological progression. In these cases, three patients received radiation for oligo-progression, and 11 patients had minor or asymptomatic progression. After discontinuing osimertinib, nine patients received carboplatin and pemetrexed chemotherapy as a subsequent therapy, two patients received no further therapy, and one patient was rechallenged with erlotinib.

**Toxicities**

Osimertinib was well tolerated, with grade 1 gastrointestinal and skin toxicity as the most common adverse effects (Table 4). Three patients required dose reduction or interruption for fatigue or gastrointestinal toxicity. One patient developed grade 4 toxicity with drug-induced pneumonitis. The symptoms improved with osimertinib discontinuation and oxygen therapy, but steroid therapy was not required. No osimertinib rechallenge was attempted.

One patient died in the hospital within 6 weeks of starting osimertinib. The cause of death was sepsis secondary to cellulitis and was not related to osimertinib or disease progression.

**Discussion**

To our knowledge, this is the first report of real-world experience in patients who received osimertinib for advanced EGFR T790M-mutant NSCLC in New Zealand. It confirms that osimertinib was well tolerated and effective in our local population.

The PFS in our cohort was comparable to that of currently published phase III data. The 12-month PFS and median PFS were 62% (95% CI: 44.8–77.5) and 14.6 months (95% CI: 12.4–16.8) in this cohort, respectively. This was favorable in comparison to the findings of the AURA3 trial (12-mo PFS 44% [95% CI: 37–51] and median PFS 10.1 mo [95% CI: 8.3–12.3]).11 Our population seemed to have a similar ORR (70%; 95% CI: 50–84) to that reported in AURA3 (71%; 95% CI: 65–76) despite including more heavily pretreated patients (24% received osimertinib as third- or fourth-line treatment). In comparison to the results of the ASTRIS real-world study of osimertinib,14 our cohort had a much smaller

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**Figure 1.** Progression-free survival. PFS, progression-free survival.

**Table 2.** EGFR T790M Mutation Testing Characteristics

| T790M Mutation Testing | Patients N = 37 |
|------------------------|----------------|
| Detection methods      |                |
| Tumor biopsy           | 30 (81%)       |
| Plasma ctDNA           | 6 (16%)        |
| Pleural cytology       | 1 (3%)         |
| Number of attempts     |                |
| 1                      | 26 (68%)       |
| 2                      | 5 (13%)        |
| 3+                     | 2 (5%)         |

ctDNA, circulating tumor DNA.

**Table 3.** Best Radiological Response to Osimertinib

| Best Responsea         | Patients n (% 95% CI) |
|------------------------|-----------------------|
| Progressive disease    | 0 (0%)                |
| Stable disease         | 11 (30%, 16–47)       |
| Partial response       | 25 (68%, 50–82)       |
| Complete response      | 1 (3%, 0–14)          |
| Overall response rate  | 26 (70%, 53–84)       |

aAs determined by descriptive radiology report, RECIST criteria not applied. N = 37.

CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors.
sample size, lower rate of plasma testing, and lower prevalence of Asian participants reflecting differences in local practice and population. Our calculated PFS and toxicity experience were similar to those of the ASTRIS, reporting a median PFS of 11.1 months (95% CI: 11-12). This trial also presented a median TTD (13.5 mo, 95% CI: 12.6–13.9) higher than the median PFS, indicating a practice of treatment beyond progression in the real-world setting. Unlike patients in AURA3 and ASTRIS, those in this study were excluded if they received less than 6 weeks of treatment with osimertinib because radiology assessment was not available.

Most of the delay in starting osimertinib was in identifying EGFR T790M mutation with the median time from disease progression to EGFR T790M mutation detection of 1.25 months (0–27). This is likely owing to scheduling and technical difficulties in obtaining a biopsy of progressing lesions. Recent recommendations suggest the use of plasma testing if available, with tumor biopsy samples used when the plasma sample result is negative or indeterminant.15 During the period of this review, plasma EGFR T790M testing was not readily available in New Zealand and was often conducted overseas and self-funded. Latterly, a local validation study provided testing for free.

Though patients with EGFR T790M-mutant NSCLC in this access program were found to have a range of ethnicities, no Māori patient was eligible to receive this effective treatment. Given the poorer cancer outcomes in this indigenous New Zealand population, further investigation is warranted to review local frequencies of EGFR mutations in Māori patients and the pathway to EGFR T790M testing.

Limitations of our study include the small sample size, retrospective data collection, and early follow-up at analysis. Furthermore, there is a potential of overestimating response rate in our cohort owing to lack of protocol-defined response assessment using the RECIST criteria. Patients reported to have responded or progressed in this cohort may have been classified as having stable disease when applying the RECIST criteria. This is a potential source of bias in the estimates of ORR and PFS.

As with most retrospective analyses, toxicity outcomes should be interpreted with caution because of the reliance on clinical documentation. Without mandated application of Common Terminology Criteria for Adverse Events criteria at the time of toxicity, it is likely that toxicity is underestimated. The low rate of osimertinib discontinuation or dose reduction reflects a favorable toxicity profile as reported in clinical trials.

## Conclusions

We conclude that osimertinib is an effective therapy in the treatment of patients in New Zealand with EGFR T790M-mutated NSCLC who have progressed after first and subsequent lines of therapy.
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