ORIGINAL ARTICLE

Real-World Response and Outcomes in Patients With NSCLC With *EGFR* Exon 20 Insertion Mutations

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ABSTRACT

Introduction: This study describes treatment patterns and outcomes in patients with NSCLC with EGFR exon 20 insertions (*EGFRex20ins*) in the United States.

Methods: The Flatiron Health electronic health record database was used to select three cohorts among patients diagnosed with NSCLC with *EGFRex20ins* (January 1, 2011–February 29, 2020): (1) first-line (1L) or patients receiving 1L therapy after documented *EGFRex20ins*; (2) second or later-line (≥2L) or patients receiving ≥2L therapy after documented *EGFRex20ins*; and (3) ≥2L postplatinum trial-aligned, or ≥2L patients previously treated with platinum chemotherapy whose baseline characteristics aligned with key eligibility criteria (initiating new treatment after documented *EGFRex20ins* and ≥1 previous treatment excluding mobocertinib or amivantamab) of the mobocertinib trial NCT02716116. Real-world end points were confirmed overall response rate, overall survival, and progression-free survival.

Results: Of 237 patients with *EGFRex20ins*-mutated NSCLC, 129 and 114 patients were included in the 1L and ≥2L cohorts, respectively. In 1L patients, platinum chemotherapy plus nonplatinum chemotherapy (31.0%) and EGFR tyrosine kinase inhibitors (28.7%) were the most common regimens. In ≥2L patients, immuno-oncology monotherapy (28.1%) and EGFR tyrosine kinase inhibitors (17.5%) were the most common index treatments. For any 1L, ≥2L, and ≥2L postplatinum trial-aligned patients, the confirmed overall response rate was 18.6%, 9.6%, and 14.0%, respectively; the median overall survival was 17.0, 13.6, and 11.5 months; the median progression-free survival was 5.2, 3.7, and 3.3 months, respectively.

Conclusions: The outcomes for patients with NSCLC with *EGFRex20ins* were poor. This real-world study provides a benchmark on treatment outcomes in this patient

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population and highlights the unmet need for improved therapeutic options.

Keywords: *EGFR* exon 20 insertions; Non–small cell lung cancer; Immunotherapy; Tyrosine kinase inhibitor therapy; Chemotherapy; Treatment outcome

Introduction

EGFR mutations are frequent in NSCLC, with an estimated prevalence of 38.8% in Asian populations, 17.4% in Caucasians, and 17.2% in African Americans.[1] Deletions in *EGFR* exon 19 or missense mutations resulting in leucine to arginine (L858R) substitution in exon 21, often referred to as classical or common *EGFR* mutations, represent approximately 85% to 90% of *EGFR* mutations.[2] Common *EGFR* mutations are associated with sensitivity to the first-generation reversible EGFR tyrosine kinase inhibitors (TKIs) gefitinib[3] and erlotinib[4] and second-generation irreversible inhibitors such as afatinib.[5] Third-generation irreversible inhibitors such as osimertinib are used to treat tumors that are sensitive to EGFR TKIs or resistant to first and second-generation agents.[6]

Rare mutations account for the remaining approximately 10% to 15% of *EGFR* mutations, and exon 20 insertions (*ex20ins*) represent approximately 4% to 12% of *EGFR*-mutated NSCLC.[7,8] *EGFRex20ins* are heterogenous at the molecular level, and clinical studies have found considerable differences in EGFR TKI sensitivity within *EGFRex20ins*. Insertions are typically located around the uninvolved residues Y764 to V769, a section that spans the final residue of the C-helix (at M766).[8] The C-helix is a key regulatory element that dictates the activation status of EGFR by rotating from an outward to an inward position, permitting specific interactions of ligands (drugs and adenosine triphosphate [ATP]) with the active site—that is, the ATP-binding pocket.[9] The specific location of the insertion can impact the rate at which drugs and ATP bind, ultimately influencing whether the cancer cells become resistant or sensitive to EGFR inhibitors.[9] Post–C-helix insertions lead to the inward displacement of the ATP-binding pocket, thereby reducing its affinity for conventional TKIs because of the insertion point being positioned at the posterior end.[10] The most common *EGFRex20ins* mutations involve the insertion of 1 to 4 amino acids after the C-helix, which collectively account for 80% to 90% of all *ex20ins* mutations.[10] Most patients with *EGFRex20ins* are resistant to first and second-generation EGFR TKIs, with reported response rates ranging from 0% to 27% and a median progression-free survival (PFS) of 3 months.[11,12] As different *EGFRex20ins* variants have varied responses to EGFR TKIs, including the third-generation inhibitor osimertinib, treatment regimens on the basis of different *EGFRex20ins* variants may be necessary for maximizing TKI efficacy.[12–15] Because of the limited clinical benefit of existing EGFR TKI, platinum-doublet chemotherapy has remained the standard of care for patients with lung cancer with *EGFRex20ins*.[12,16,17]

Currently, only two drugs, amivantamab (Rybrevant) and mobocertinib (Exkivity), are approved for patients with NSCLC with *EGFRex20ins*.[18,19] Both agents are indicated as second-line therapy for patients with disease progression after previous platinum-based chemotherapy.[20] Amivantamab is a fully human intravenous EGFR mesenchymal-epithelial transition factor bispecific antibody with immune cell–directing activity.[21] Amivantamab can inhibit receptor-ligand binding, promote receptor-antibody complex endocytosis and degradation, and induce Fc-dependent trogocytosis by macrophages and antibody-dependent cellular cytotoxicity by natural killer cells.[21] Mobocertinib is a novel, first-in-class, irreversible oral TKI designed to selectively target *EGFR* and *HER2* exon 20 insertion mutants.[22] In a single-arm phase 1/2 nonrandomized clinical trial evaluating the safety, pharmacokinetics, and antitumor activity of mobocertinib in patients with NSCLC with *EGFRex20ins* and who were previously treated with platinum-based chemotherapy (NCT02716116), mobocertinib (160 mg once daily) led to an investigator-assessed confirmed overall response rate (cORR) of 35.1% (95% confidence interval [CI]: 26.4–44.6), median PFS of 7.3 (95% CI: 5.6–8.8) months, median overall survival (OS) of 20.2 (95% CI: 14.9–25.3) months, and time to treatment discontinuation of 7.4 (95% CI: 6.4–8.5) months.[18,23,24]

Findings from clinical trials may be supported by analyses of real-world data, especially in rare patient populations such as those with NSCLC with *EGFRex20ins*, in which conducting controlled trials with a comparator arm is difficult. The objective of this study was to contextualize the findings of the mobocertinib trial (NCT02716116)[23] and gain insight into the treatment patterns and clinical outcomes in patients with NSCLC with *EGFRex20ins* in the first- and subsequent-line settings.

Materials and Methods

Data Source

Data for this analysis were extracted from the Flatiron Health database, a U.S. nationwide, demographically

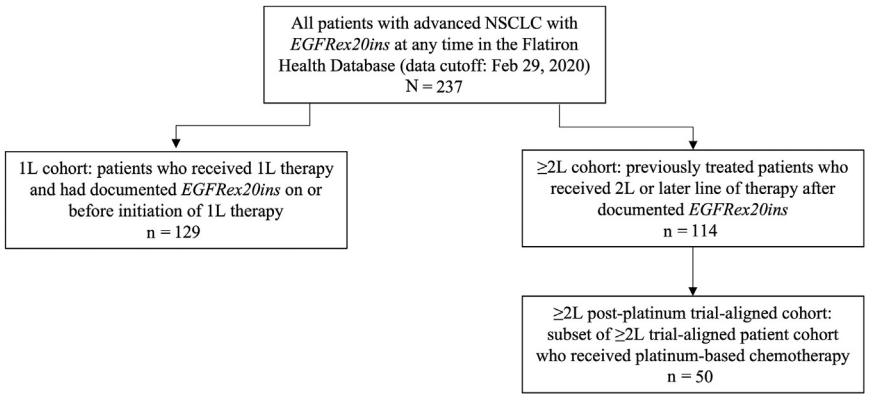

Figure 1. Patient attrition for study cohorts. Patients could have been included in more than one cohort on the basis of the lines of treatment received. ≥2L, second-or-later-line; 1L, first-line; EGFRex20ins, EGFR exon 20 insertion.

and geographically diverse, deidentified, patient-level, electronic health record–derived database. At the time of this research, the Flatiron Health database comprised data from over 280 cancer clinics representing more than 2.2 million active patients with cancer in the United States treated at over 800 unique sites of care.[25] The longitudinal, de-identified data set delivers a wide pool of data, including patient demographics, treatment, and clinical outcomes.[26] The electronic health record includes structured data (e.g., laboratory values, prescribed drugs) and unstructured data (e.g., physician's notes, biomarker reports) collected by means of technology-enabled chart abstraction.[26]

Patients diagnosed with locally advanced or metastatic NSCLC with *EGFRex20ins* mutations on or after January 1, 2011 were eligible for this study. All available data in the Flatiron Health database were used. The data cutoff was February 29, 2020.

Study Design

This retrospective, observational cohort study was conducted among patients aged 18 years and older with confirmed locally advanced or metastatic NSCLC (stage IIIB–IV) with *EGFRex20ins*. The study included three cohorts (Fig. 1). The first-line (1L) cohort included patients who received 1L therapy for advanced NSCLC after documented *EGFRex20ins*. The second or later-line (≥2L) cohort included patients who initiated a new treatment after they had a confirmed diagnosis of advanced NSCLC, their tumors tested positive for *EGFRex20ins*, and they had previously received at least one line of therapy in the advanced setting. The ≥2L postplatinum trial-aligned cohort was a subgroup of ≥2L patients (as defined above) who had been previously treated with platinum chemotherapy and had not previously received mobocertinib or amivantamab. Their baseline characteristics were aligned with the key eligibility criteria of the mobocertinib phase 1/2 pivotal trial (Supplementary Table 1).[23] Patients were required to have documented *EGFRex20ins* mutations at the time of cohort entry to avoid the bias because of the immortal time period (i.e., patients had to be alive until their *EGFRex20ins* were tested). The index date for the 1L patient cohort was defined as the start date of 1L therapy. The index date for the ≥2L and ≥2L post-platinum trial-aligned cohorts was defined as the start date of the new treatment initiated immediately after a confirmed diagnosis of locally advanced or metastatic NSCLC, a documented *EGFRex20ins*, and at least one previous line of therapy in the advanced setting.

Baseline Demographics and Clinical Characteristics

Demographic and clinical characteristics were assessed on the index date. Demographic characteristics included age, sex, race, smoking status, and year of first diagnosis. Clinical characteristics included cancer stage, time from the initial diagnosis to the index date, histologic diagnosis, site of metastasis, Eastern Cooperative Oncology Group performance status (ECOG PS), test type used to detect *EGFR* mutation and previous advanced NSCLC therapy.

Treatment Patterns

Treatment agents of the index line of therapy were categorized by therapy type, which included platinum chemotherapy, nonplatinum chemotherapy, monoclonal antibody, EGFR TKI, immuno-oncology (IO) therapy, and other therapies.

Clinical Outcomes

The primary outcome was a real-world confirmed overall response rate (rwORR). Confirmed rwORR was defined as the proportion of patients who achieved real-

Table 1. Patient Baseline Demographic and Clinical Characteristics

Characteristics	1L Cohort n = 129	≥2L Cohort n = 114	≥2L Postplatinum Trial-Aligned Cohort n = 50
Age (y)			
Mean (SD)	65.2 (11.2)	65.2 (10.7)	64.3 (10.3)
Median	66.0	65.5	64.0
Min, max	38, 84	38, 84	40, 83
Age category, n (%)			
18-64 y	62 (48.1)	53 (46.5)	25 (50.0)
≥65 y	67 (51.9)	61 (53.5)	25 (50.0)
Sex, n (%)			
Male	45 (34.9)	45 (39.5)	16 (32.0)
Female	84 (65.1)	69 (60.5)	34 (68.0)
Race, n (%)			
Asian	9 (7.0)	11 (9.6)	4 (8.0)
Non-Asian	109 (84.5)	96 (84.2)	44 (88.0)
Missing	11 (8.5)	7 (6.1)	2 (4.0)
History of smoking, n (%)			
Yes	66 (51.2)	56 (49.1)	21 (42.0)
No	63 (48.8)	58 (50.9)	29 (58.0)
Cancer stage at initial NSCLC diagnosis, n (%)			
Stage I	12 (9.3)	11 (9.6)	5 (10.0)
Stage II	7 (5.4)	5 (4.4)	2 (4.0)
Stage III	12 (9.3)	18 (15.8)	7 (14.0)
Stage IV	98 (76.0)	80 (70.2)	36 (72.0)
Time from initial NSCLC diagnosis to the index date (mo)			
Mean (SD)	8.1 (15.5)	19.2 (27.6)	17.2 (20.3)
Median	1.5	10.8	11.1
Min, max	0.2, 91.5	1.4, 214.1	1.9, 98.2
Histologic diagnosis, n (%)			
Adenocarcinoma	123 (95.3)	111 (97.4)	49 (98.0)
Adenosquamous	2 (1.6)	1 (0.9)	-
Squamous cell carcinoma	4 (3.1)	2 (1.8)	1 (2.0)
Site of metastasis,[a] n (%)			
Brain	38 (29.5)	39 (34.2)	17 (34.0)
Liver	19 (14.7)	31 (27.2)	14 (28.0)
Bone	66 (51.2)	60 (52.6)	26 (52.0)
Other	83 (64.3)	81 (71.1)	30 (60.0)
None	13 (10.1)	10 (8.8)	8 (16.0)
ECOG PS,[b] n (%)			
0	30 (23.3)	23 (20.2)	8 (16.0)
1	36 (27.9)	41 (36.0)	21 (42.0)
2	6 (4.7)	13 (11.4)	-
3	1 (0.8)	4 (3.5)	-
Missing	56 (43.4)	33 (28.9)	21 (42.0)
Biomarkers,[c] n (%)			
ALK	1 (0.8)	1 (0.9)	-
PD-L1	41 (31.8)	34 (29.8)	10 (20.0)
KRAS	1 (0.8)	-	-
Type of EGFR mutation,[c] n (%)			
Exon 19 deletion, Exon 20 insertion, Other	1 (0.8)	-	-
Exon 20 insertion	122 (94.6)	108 (94.7)	48 (96.0)
Exon 20 insertion, L858R	1 (0.8)	1 (0.9)	-
Exon 20 insertion, other	3 (2.3)	4 (3.5)	2 (4.0)
Exon 20 insertion, unknown	2 (1.6)	1 (0.9)	-
EGFRex20ins detection method, n (%)			
NGS	48 (37.2)	49 (43.0)	19 (38.0)
PCR	33 (25.6)	29 (25.4)	15 (30.0)
Other sequencing method	37 (28.7)	29 (25.4)	14 (28.0)
Other	1 (0.8)	1 (0.9)	-
Unknown	10 (7.8)	6 (5.3)	2 (4.0)

(continued)

Table 1. Continued

Characteristics	1L Cohort n = 129	≥2L Cohort n = 114	≥2L Postplatinum Trial-Aligned Cohort n = 50
No. of previous lines, n (%)			
1	-	105 (92.1)	48 (96.0)
2	-	5 (4.4)	1 (2.0)
≥3	-	4 (3.5)	1 (2.0)
Previous use of EGFR TKI, n (%)			
Yes	-	19 (16.7)	1 (2.0)
No	129 (100.0)	95 (83.3)	49 (98.0)
Previous use of IO therapy, n (%)			
Yes	-	18 (15.8)	2 (4.0)
No	129 (100.0)	96 (84.2)	48 (96.0)
Previous use of chemotherapy, n (%)			
Yes	-	88 (77.2)	50 (100.0)
No	129 (100.0)	26 (22.8)	-

[a]Site of metastasis does not have mutually exclusive categories.
[b]ECOG PS was assessed within 3 months before the index date.
[c]Reported when positive at any time before or on index date.
≥2L, second-or-later-line; 1L, first-line; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFRex20ins, EGFR exon 20 insertion; IO, immuno-oncology; Max, maximum; Min, minimum; NGS, next-generation sequencing; PCR, polymerase chain reaction; PD-L1, programmed death-ligand 1; TKI, tyrosine kinase inhibitor.

world confirmed response among all patients in that cohort. Patients were considered to achieve real-world confirmed response when they had a partial response (PR) or complete response (CR) assessment determination on the basis of clinician interpretation of change in disease burden after radiology scan(s), followed by a subsequent assessment of PR, CR, or stable disease during the course of a single line of therapy.

The secondary outcomes included OS and real-world PFS (rwPFS). OS was defined as the time from the index date to death. Patients for whom a date of death was not identified were censored at the date of last confirmed activity. rwPFS was defined as the time from the index date to real-world progression or death from any cause; patients with no evidence of documented progression were censored at the end-of-line of therapy or last clinic note date, whichever was earlier.

Statistical Analysis

The treatment type was summarized using descriptive statistics, frequencies, and percentages. Confirmed rwORR was calculated as the number of patients with at least one PR or CR determination followed by a subsequent PR, CR, or stable disease determination, of any duration divided by the total number of patients in that cohort. Time-to-event end points (OS and rwPFS) were assessed using the Kaplan-Meier (KM) method and were reported as median and 95% CIs. Posthoc analyses were conducted to assess the effectiveness of chemotherapy, IO therapy, and EGFR TKIs using rwORR, rwPFS, and OS among patients in the 1L and ≥2L cohorts.

Results

Baseline Demographic and Clinical Characteristics

Patient attrition is presented in Figure 1. A total of 237 patients with advanced NSCLC with *EGFRex20ins* were identified in the Flatiron Health database. There were 129 patients in the 1L cohort and 114 patients in the ≥2L cohort, of whom 50 patients were included in the ≥2L postplatinum trial-aligned cohort.

Patient baseline demographic and clinical characteristics are summarized in Table 1. Demographics and baseline characteristics of the patients in the platinum-pretreated patients of the NCT02716116 trial[27] are presented in Supplementary Table 2. Across cohorts, the mean (SD) patient age ranged from 64.3 (10.26) to 65.2 (11.19) years, the proportion of women ranged from 60.5% to 68.0%, the proportion of non-Asian patients ranged from 84.2% to 88.0%, and the proportion of patients with a history of smoking ranged from 42.0% to 51.2%. Most (>95%) patients had adenocarcinoma, approximately one-third of patients presented with brain metastasis, and 70.2% to 76.0% of patients had stage IV NSCLC at initial diagnosis. The proportion of patients with ECOG PS of 0 to 1 ranged from 51.2% to 61.9%; data for ECOG PS were missing for 28.9% to 43.4% of patients. The most typically used *EGFRex20ins* detection method was next-generation sequencing, with 37.2% to 43.0% of tests conducted using this technology. Polymerase chain reaction, with 25.4% to 30.0% of tests, and other sequencing methods, with 25.4% to 28.7% of tests, were also frequently performed.

Table 2. Treatment Patterns of Index Therapy[a]

Index Line of Therapy, n (%)[b]	1L Cohort n = 129	≥2L Cohort n = 114	≥2L Postplatinum Trial-Aligned Cohort n = 50
EGFR TKI	37 (28.7)	20 (17.5)	10 (20.0)
EGFR TKI + mAb	1 (0.8)	-	-
IO monotherapy	11 (8.5)	32 (28.1)	20 (40.0)
Nonplatinum chemo	3 (2.3)	13 (11.4)	7 (14.0)
Nonplatinum chemo + mAb	1 (0.8)	11 (9.6)	4 (8.0)
Nonplatinum chemo + IO therapy	-	1 (0.9)	-
Platinum chemo	1 (0.8)	1 (0.9)	-
Platinum chemo + nonplatinum chemo	40 (31.0)	13 (11.4)	5 (10.0)
Platinum chemo + nonplatinum chemo + mAb	16 (12.4)	6 (5.3)	1 (2.0)
Platinum chemo + nonplatinum chemo + IO therapy	16 (12.4)	7 (6.1)	3 (6.0)
Other therapy	3 (2.3)[c]	10 (8.8)[d]	-

[a]The individual EGFR TKIs received are presented in Supplementary Table 4.
[b]Most typically used nonplatinum chemotherapy was pemetrexed in 1L and ≥2L settings.
[c]One patient received alectinib, one patient received crizotinib, and one patient received bortezomib and cyclophosphamide.
[d]Nine patients received regimens containing a clinical study drug; one patient received cetuximab.
1L, first-line; ≥2L, second-or-later-line; Chemo, chemotherapy; IO, immune-oncology; mAb, monoclonal antibody; TKI, tyrosine kinase inhibitor.

Treatment Patterns

Treatment patterns of index therapy are presented in Table 2. Among patients in the 1L cohort, the most frequently observed index therapy was platinum chemotherapy plus nonplatinum chemotherapy (31.0%), followed by EGFR TKI (28.7%), platinum chemotherapy plus nonplatinum chemotherapy plus IO therapy (12.4%), or platinum chemotherapy plus nonplatinum chemotherapy plus monoclonal antibody (12.4%). Among patients in the ≥2L cohorts, IO monotherapy was the most frequent index therapy (28.1%), followed by EGFR TKI (17.5%), platinum chemotherapy plus nonplatinum chemotherapy (11.4%), and nonplatinum chemotherapy (11.4%). Treatment patterns were similar between the ≥2L and ≥2L postplatinum trial-aligned cohorts.

Clinical Outcomes

1L Cohort. Table 3 summarizes the clinical outcomes of patients in the 1L cohort. Among 129 patients in this cohort, 24 achieved a confirmed response, with an rwORR of 18.6% (95% CI: 12.3%, 26.4%). The median OS was 17.0 months (95% CI: 11.2–19.5) (Fig. 2*A*), and the median rwPFS was 5.2 months (95% CI: 3.1–6.9) (Fig. 3*A*). Similar outcomes were observed in patients receiving platinum chemotherapy (n = 41) or platinum chemotherapy combined with IO (n = 16), with confirmed rwORRs of 19.5% and 18.8%, respectively. Patients treated with IO monotherapy (n = 11) or EGFR TKI monotherapy (excluding mobocertinib; n = 37) experienced poorer outcomes, with confirmed rwORRs of 9.1% and 2.7%, respectively. KM curves for OS and rwPFS by treatment type are illustrated in Supplementary Figures 1 and 2. Patients treated with osimertinib monotherapy in the 1L setting (n = 6) had a cORR of 0%.

Greater Than or Equal to 2L and Greater Than or Equal to 2L Postplatinum Trial-Aligned Cohorts. Table 4 summarizes the clinical outcomes of patients in the ≥2L and ≥2L postplatinum trial-aligned cohorts. In the ≥2L and ≥2L postplatinum trial-aligned cohorts, 11 and 7 patients achieved confirmed response with a confirmed rwORR of 9.6% (95% CI: 4.9%–16.6%) and 14.0% (95% CI: 5.8%–26.7%), respectively. The ≥2L cohort had a median OS of 13.6 months (95% CI: 8.2–15.4) (Fig. 2*B*) and a median rwPFS of 3.7 months (95% CI: 2.7–5.2) (Fig. 3*B*). Similarly, the ≥2L postplatinum trial-aligned cohort had a median OS of 11.5 months (95% CI: 7.9–16.6) (Fig. 2*C*) and a median rwPFS of 3.3 months (95% CI: 2.3–5.9) (Fig. 3*C*). In the ≥2L setting, patients treated with postplatinum chemotherapy had a confirmed rwORR of 16.1%, whereas those treated with IO or EGFR TKIs had poor responses (confirmed rwORR: 3.1% and 5.0%, respectively). No clinical benefit was seen in patients who used osimertinib monotherapy in the ≥2L setting (n = 7), with a cORR of 0%. KM curves for OS and rwPFS by treatment type are illustrated in Supplementary Figures 3 and 4.

IO Therapy and PD-L1 Status. For patients who received IO monotherapy as 1L or ≥2L treatment, the confirmed rwORR was 5.0% (95% CI: 0.1%–24.9%) for those with positive programmed death-ligand 1 (PD-L1) status (defined as PD-L1 expression ≥1% or reported as positive, n = 20) and 4.3% (95% CI: 0.1%–22.0%) for patients with a negative or unknown PD-L1 status (n = 23) (Supplementary Table 3).

Discussion

This study described treatment patterns and clinical outcomes among patients with advanced NSCLC with *EGFRex20ins* who received first or subsequent treatment

Table 3. Clinical Outcomes in First-Line

1L Therapy	n	Confirmed rwORR, % (95% CI)	OS (mo), Median (95% CI)	rwPFS (mo), Median (95% CI)
Any 1L therapy	129	18.6 (12.3-26.4)	17.0 (11.2-19.5)	5.2 (3.1-6.9)
1L treatment type				
Platinum chemotherapy[a]	41	19.5 (8.8-34.9)	17.0 (10.5-33.2)	5.7 (3.0-10.9)
IO + platinum chemotherapy	16	18.8 (4.0-45.6)	11.3 (5.6-NE)	4.5 (1.2-10.3)
IO monotherapy	11	9.1 (0.2-41.3)	11.0 (1.2-NE)	3.1 (1.1-5.2)
EGFR TKI monotherapy	37	2.7 (0.1-14.2)	10.7 (3.4-22.3)	3.3 (2.2-6.6)

[a]Platinum-based chemotherapy plus or minus nonplatinum-based chemotherapy.
1L, first-line; CI, confidence interval; IO, immuno-oncology; NE, not estimable; OS: overall survival; rwORR, real-world overall response rate; rwPFS: real-world progression-free survival; TKI, tyrosine kinase inhibitor.

for advanced NSCLC. Consistent with previous studies, a diversity of available therapies for treating NSCLC with *EGFRex20ins*, including chemotherapy, IO, and EGFR TKIs approved for common *EGFR* mutations, was observed with a lack of effective treatment options.[17,27–30] These treatments were associated with low response rates and modest outcomes among 1L patients (confirmed rwORR: 18.6%, OS: 17.0 mo, rwPFS: 5.2 mo), and in previously treated patients (confirmed rwORR: 9.6%–14.0%, OS: 11.5–13.6 mo, rwPFS: 3.3–3.7 mo), emphasizing the unmet need for new therapies with improved potency against NSCLC with *EGFRex20ins*. The recent approvals of amivantamab (ORR: 40%, PFS: 8.3 mo, OS: 22.8 mo) and mobocertinib (ORR: 28%, PFS: 7.3 mo, OS: 24.0 mo) with clinically meaningful efficacy and favorable safety profiles in patients with NSCLC with *EGFRex20ins* previously treated with platinum-based chemotherapy provide potential treatment options in this patient population.[20]

In this study, patients treated with 1L platinum-based chemotherapy had a confirmed rwORR of 19.5%, a median OS of 17.0 months, and a median rwPFS of 5.7 months. This is consistent with previous retrospective studies (2009–2020) conducted in the People's Republic of China, France, Japan, Korea, and the United States that found response rates for platinum systemic chemotherapy in the 1L setting can range from 11.8% to 63%, with a median OS of 18.2 months to 3.2 years and a median PFS of 4 to 8.9 months.[12,16,17,28,31]

This study also found that 1L IO treatment, either as monotherapy or in combination with chemotherapy, was associated with a low confirmed rwORR of 9.1% and 18.8%, a median OS of 11.0 months and 11.3 months, and a median rwPFS of 3.1 and 4.5 months, respectively. The effectiveness of IO therapy among previously treated patients was also low, with a confirmed rwORR of 3.1%, a median OS of 8.1 months, and a median rwPFS of 2.3 months. Results from previous studies on the effectiveness of IO agents for patients with NSCLC with *EGFRex20ins* are varied. Most phase 2/3 studies assessing chemotherapy plus IO as 1L and ≥2L treatments excluded patients with NSCLC with sensitizing *EGFRex20ins*.[32–34] Real-world evidence on the effectiveness of IO therapy is on the basis of small studies ($n < 10$) and case reports in single patients with NSCLC with *EGFRex20ins* treated with IO alone or in combination with chemotherapy. Some of these studies reported an association between uncommon *EGFR* mutations, including exon 20 insertions, and superior response to IO therapy compared with common *EGFR* mutations, long-term survival (≥5 y), and disease control in treatment-naive and heavily pretreated patients and those with brain metastases.[35–37] Other retrospective analyses (2009–2019) conducted in the People's Republic of China, Italy, Japan, and the United States reported that IO therapy is a common treatment strategy for patients with NSCLC with *EGFRex20ins*; however, it was associated with low response rates (0%–22.2%) and poor prognosis (median OS: 1.6–10.2 mo, median PFS: 1.5–10 mo).[17,28,36,38,39] According to National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (National Comprehensive Cancer Network Guidelines), the preferred systemic therapy for advanced or metastatic NSCLC (adenocarcinoma, large cell, NSCLC not otherwise specified [PS 0–1]) with *EGFRex20ins* is pembrolizumab plus carboplatin plus pemetrexed or pembrolizumab plus cisplatin plus pemetrexed with the lack of contraindications to programmed cell death protein-1 (PD-1) or PD-L1 inhibitors.[40] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease or current use of immunosuppressive agents or both, or the presence of an oncogene (e.g., *EGFR exon 19* deletion or *L858R*, *ALK* rearrangements), which would predict lack of benefit.[40]

PD-L1 expression represents a predictive biomarker of the likelihood of response to IO therapy with PD-1 inhibitors.[41,42] Previous studies report that up to 61% of NSCLC tumors with *EGFRex20ins* have more than 1% of tumor cells considered positive for PD-L1 expression, with levels of PD-L1 varying according to different *EGFRex20ins* variants.[43,44] In the present study, response rates among patients receiving IO monotherapy in the

	1L cohort N=129	≥2L cohort N=114	≥2L post-platinum trial-aligned cohort N=50
OS (months), median (95% CI)	17.0 (11.2–19.5)	13.6 (8.2–15.4)	11.5 (7.9–16.6)

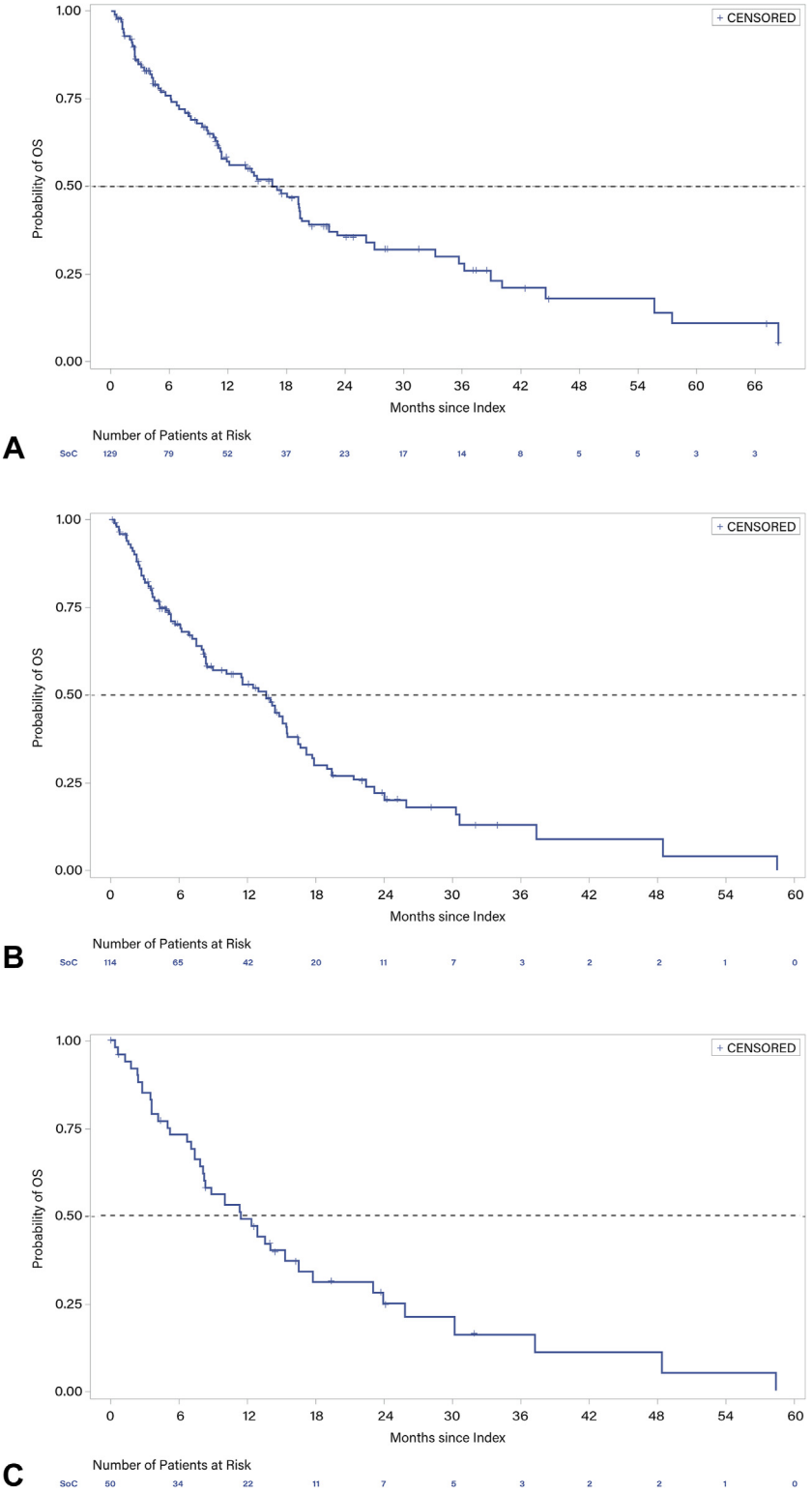

Figure 2. OS. (*A*) 1L cohort; (*B*) ≥2L cohort; (*C*) ≥2L postplatinum trial-aligned cohort. Note: Patients could have been included in more than one cohort on the basis of the lines of treatment received. ≥2L, second-or-later-line; 1L, first-line; CI, confidence interval; OS, overall survival.

	1L cohort N=129	≥2L cohort N=114	≥2L post-platinum trial-aligned cohort N=50
rwPFS, median (95% CI)	5.2 (3.1, 6.9)	3.7 (2.7, 5.2)	3.3 (2.3, 5.9)

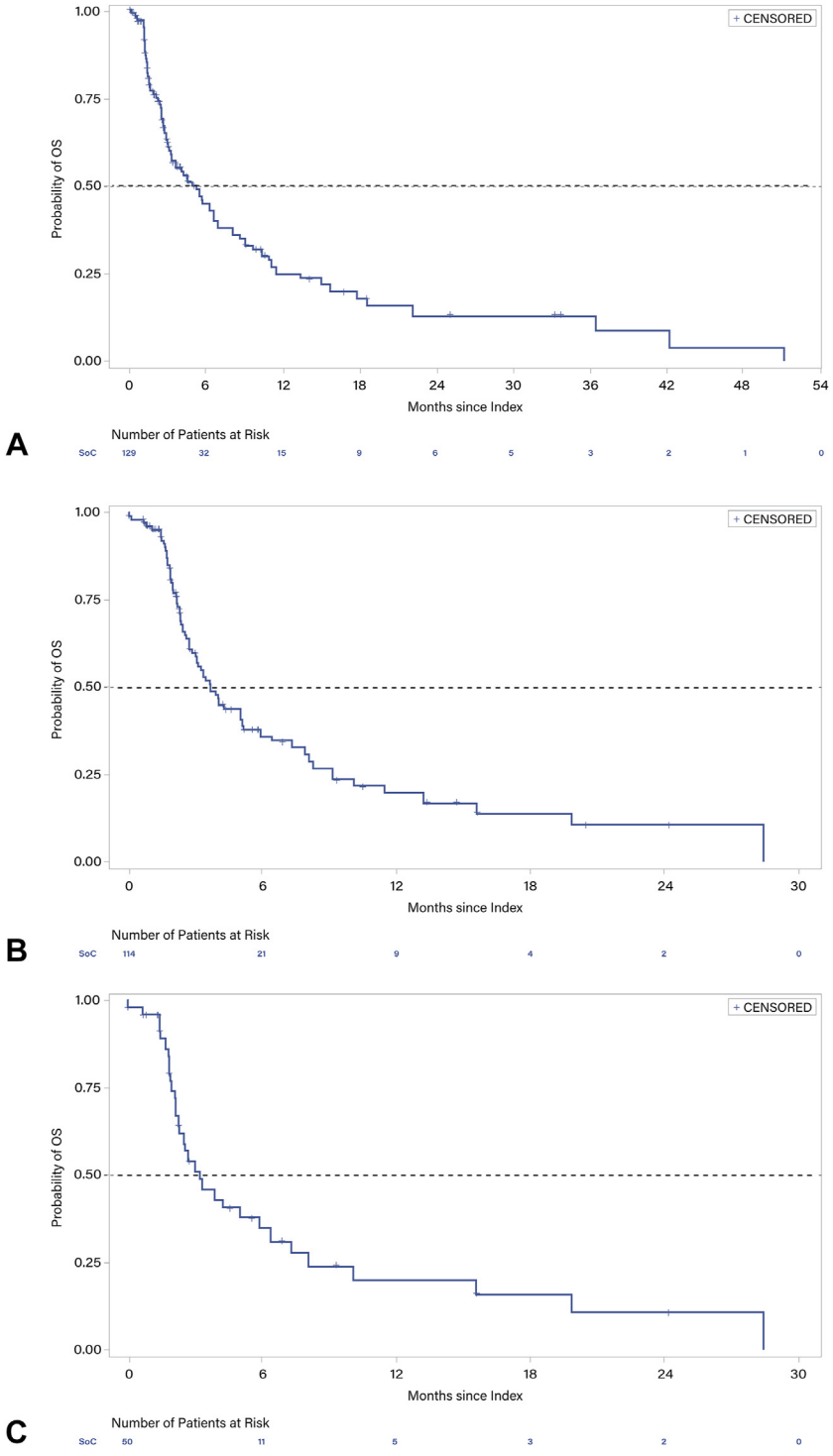

Figure 3. rwPFS. (*A*) 1L cohort; (*B*) ≥2L cohort; (*C*) ≥2L postplatinum trial-aligned cohort. Note: Patients could have been included in more than one cohort on the basis of the lines of treatment received. ≥2L, second-or-later-line; 1L, first-line; CI, confidence interval; rwPFS, real-world progression-free survival.

Table 4. Clinical Outcomes in Second or Later Lines

≥2L Therapy	n	Confirmed rwORR, % (95% CI)	OS (mo), Median (95% CI)	rwPFS (mo), Median (95% CI)
Any ≥2L therapy	114	9.6 (4.9-16.6)	13.6 (8.2-15.4)	3.7 (2.7-5.2)
Any ≥2L therapy in postplatinum trial-aligned patients	50	14.0 (5.8-26.7)	11.5 (7.9-16.6)	3.3 (2.3-5.9)
≥2L treatment type				
Postplatinum chemotherapy	31	16.1 (5.5-33.7)	13.9 (8.2-24.0)	5.0 (2.9-10.1)
IO monotherapy	32	3.1 (0.1-16.2)	8.1 (2.9-15.0)	2.3 (1.9-3.7)
EGFR TKI monotherapy	20	5.0 (0.1-24.9)	11.5 (3.7-15.3)	3.1 (1.7-3.9)

2L, second-line; CI, confidence interval; IO, immuno-oncology; NE, not estimable; OS: overall survival; rwORR, real-world overall response rate; rwPFS: real-world progression-free survival; TKI, tyrosine kinase inhibitor.

first or later-line of therapy were low (≤5%) and outcomes were poor (OS: 6.1–8.9 mo, PFS: 2.3–2.5 mo) regardless of PD-L1 expression, suggesting that IO therapy was not effective for patients with NSCLC with *EGFRex20ins* and positive PD-L1 status. These findings are consistent with a retrospective analysis evaluating the clinicopathologic characteristics of patients with NSCLC with *EGFRex20ins* treated with IO therapy that found no difference in survival on the basis of PD-L1 expression status.[38]

The poor activity of all-generation EGFR TKIs approved for the treatment of NSCLC with common EGFR mutations as any line of therapy in patients with NSCLC with *EGFRex20ins* has previously been described in retrospective studies (2009–2019) conducted in the United States and the People's Republic of China, with response rates of 0% to 33%, median PFS of 1.8 to 5 months, and a median OS of 7.1 to 16.8 months.[17,28,30] In the present study, treatment with any generation EGFR TKI was observed to have a limited clinical benefit, regardless of line of therapy. Among patients initiating EGFR TKI as 1L therapy, rwORR was 2.7%, the median OS was 10.7 months, and the median rwPFS was 3.3 months. For previously treated patients receiving EGFR TKI as index therapy, rwORR was 5%, the median OS was 11.5 months, and the median rwPFS was 3.1 months. As earlier-generation EGFR TKIs are largely ineffective in patients with NSCLC with *EGFRex20ins*, newer agents are being developed to overcome resistance to EGFR-directed therapies in tumors with *EGFRex20ins*.[9] A previous study reported a cORR of 25% and a median PFS of 9.7 months among 21 patients with one or more previous lines of therapy for osimertinib, the latest third-generation EGFR TKI to be approved for NSCLC with *EGFR* exon 19 deletions or exon 21 L858R mutations.[14] Another study observed promising antitumor activity of osimertinib against NSCLC tumors with specific *EGFRex20ins* variants with patients achieving PR and stable disease and a median PFS of 6.2 months.[13] In the present study, the cORR of osimertinib was 0% in both the 1L (n = 6) and ≥2L (n = 7) setting, which aligns more closely with reports of ORR of 5% to 6.5%, and a median PFS of 2.3 months among patients receiving osimertinib primarily as 2L therapy postplatinum chemotherapy.[15,45] In one of these studies, only two patients received high-dose osimertinib (160 mg), and neither patient exhibited a radiologic response.[15] Although *EGFRex20ins* variant data were not available in the present study and the sample size was small, these findings suggest osimertinib may have limited antitumor activity against diverse *EGFRex20ins*.

Considering the poor responses and modest outcomes of typically used therapies for NSCLC with *EGFRex20ins*, there is a need for more effective treatment options. Recent approvals of amivantamab and mobocertinib with illustrated clinical benefits across various *EGFRex20ins* variants despite different mechanisms of action hold the promise of improved patient outcomes. These agents warrant the education of physicians involved in NSCLC diagnosis and treatment to ensure patients are tested for *EGFRex20ins* and benefit from these targeted therapies.

This study has limitations inherent to any real-world retrospective analysis. The real-world outcomes in this study were defined as accurately as possible on the basis of available data and following the rigorous procedures in place at Flatiron Health; however, data collection in the real-world setting may not be uniform. There is potential for variability and subjectivity of reported outcomes as assessments of treatment response are on the basis of the clinician's interpretation of change in disease burden after radiology scan(s) and not on standard criteria such as Response Evaluation Criteria in Solid Tumors. Patients may be assessed less frequently in the real world compared with clinical trial settings, which could result in surveillance bias, delayed or even nonidentification of disease progression, and overestimation of rwPFS and rwDOR. Effects of patient-level factors, including age,[46] smoking status,[47] and sex,[48] which impact the frequency

of *EGFRex20ins* and choice of treatment, were not accounted for in the present study. ECOG PS is a known predictor of outcomes in patients with cancer,[49] yet these data were missing for a large proportion of the ≥2L patients. This study had a small sample size; therefore, outcome estimates tended to have large variances. Patients in the study were largely from the community setting in the United States, and outcomes such as treatment patterns may not be generalizable to patients treated in an academic setting or outside of the United States where prescribing practices may vary. *EGFRex20ins* are known to be heterogenous[7,17,50]; however, *EGFRex20ins* variant data were not captured in the Flatiron Health database. Patients may have sought care elsewhere, with data not available from the Flatiron database. The study period was from 2011 to 2020, during which the diagnostic and treatment landscape changed vastly; notably, most of the patients in this study had a diagnosis after 2015.

To conclude, in real-world settings, treatment patterns are diverse in patients with advanced NSCLC with *EGFRex20ins*. Chemotherapy regimens and EGFR TKIs were the most typically received treatments for 1L therapy, followed by IO alone or in combination with chemotherapy. Regimens containing chemotherapy and IO were the most typically used therapy among previously treated patients, with EGFR TKIs also frequently used. Clinical outcomes were poor among patients with advanced NSCLC with *EGFRex20ins*. IO therapy, either as monotherapy or in combination with chemotherapy, seemed to be the least effective option for the treatment of NSCLC with *EGFRex20ins*. EGFR TKI treatment had limited clinical benefits in patients with *EGFRex20ins* in the 1L and ≥2L settings. These data serve as a benchmark for treatment outcomes in patients with NSCLC with *EGFRex20ins* and reveal an unmet need for improved therapeutic options for this population.

CRediT Authorship Contribution Statement

Sai-Hong I. Ou: Conceptualization, Investigation, Roles/Writing – original draft, Writing – review & editing.

Huamao M. Lin: Conceptualization, Methodology, Supervision, Writing – review & editing.

Jin-Liern Hong: Conceptualization, Methodology, Writing – review & editing.

Yu Yin: Conceptualization, Data curation, Formal analysis, Methodology, Software, Validation, Writing - review & editing.

Shu Jin: Conceptualization, Data curation, Writing – review & editing.

Jianchang Lin: Formal analysis, Methodology, Writing – review & editing.

Minal Mehta: Data curation, Validation, Writing - review & editing.

Danny Nguyen: Investigation, Writing – review & editing.

Joel W. Neal: Investigation, Supervision, Validation, Writing – review & editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100558.

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