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Comparative clinical outcomes for patients with advanced NSCLC harboring *EGFR* exon 20 insertion mutations and common *EGFR* mutations

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ABSTRACT

Introduction: Real-world clinical outcomes in patients with advanced NSCLC harboring *EGFR* exon 20 insertion (*exon20ins*) mutations have not been extensively studied. We conducted a retrospective cohort study to assess the clinical outcomes of *EGFR exon20ins* compared with common *EGFR* (*cEGFR*) mutations.

Methods: Adults with advanced NSCLC harboring any *EGFR* mutations in the NSCLC Flatiron registry (2011 through May 2020) were included. To compare the relative prognosis (prognostic value) of *exon20ins* vs *cEGFR*, real-world overall survival (rwOS) was the primary endpoint. Separately, to compare the relative response to tyrosine kinase inhibitor (TKI) treatment (predictive value), real-world progression-free survival (rwPFS) was the primary endpoint.

Results: For the prognostic value analysis, 3014 patients with *EGFR* mutant NSCLC (*cEGFR*, n = 2833; *EGFR exon20ins*, n = 181) were eligible. The median (95% CI) rwOS was 16.2 (11.04–19.38) months in the *EGFR exon20ins* cohort vs 25.5 (24.48–27.04) months in the *cEGFR* cohort (adjusted HR, 1.75 [1.45–2.13]; $p < 0.0001$); 5-year rwOS was 8% and 19%, respectively. For the predictive value analysis, 2825 patients received TKI treatment and were eligible (*cEGFR*, n = 2749; *EGFR exon20ins*, n = 76). The median (95% CI) rwPFS from start of the first TKI was 2.9 (2.14–3.91) months in the *EGFR exon20ins* cohort vs 10.5 (10.05–10.94) months in the *cEGFR* cohort (adjusted HR, 2.69 [2.05–3.54]; $p < 0001$). Among patients with *EGFR exon20ins*, the most common prescribed first-line therapy was platinum-based chemotherapy (61.3%) followed by EGFR TKIs (21.5%); second-line treatments were varied, with no clear standard of care.

Conclusions: Patients with *EGFR exon20ins* have poor prognosis and receive little benefit from EGFR TKI treatment. More effective therapies are needed in this difficult-to-treat population.

Abbreviations: cEGFR, common EGFR mutations; exon20ins, exon 20 insertion mutations; IO, immunotherapy; NOS, not otherwise specified; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; rwTTNT, real-world time to next therapy.

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1. Introduction

In patients with advanced NSCLC harboring exon 19 deletions or L858R substitution mutations in the epidermal growth factor receptor (*EGFR*) gene, treatment with EGFR tyrosine kinase inhibitors (TKIs) has demonstrated improvement in progression-free survival (PFS)[1–5] and overall survival (OS)[6] compared with chemotherapy. These 2 mutation types, referred to here as common *EGFR* mutations (*cEGFR*), constitute approximately 80% to 90% of all *EGFR* mutations.[7–9] Clinical trials of the first-generation EGFR TKIs gefitinib and erlotinib [2,3,10–13] and second-generation EGFR TKI afatinib [4–6] in patients with advanced NSCLC harboring *cEGFR* have shown a median PFS ranging from 8.0 to 13.6 months and a median OS ranging from 19.3 to 33.3 months. Recent results from the FLAURA study assessing the third-generation EGFR TKI osimertinib in patients with *cEGFR* demonstrated a median PFS of 18.9 months and a median OS of 38.6 months.[14,15]

In contrast, *EGFR* exon 20 insertion mutations (*exon20ins*), which comprise up to 12% of *EGFR* mutations in patients with NSCLC,[7–9] have not been extensively studied, and the available information on treatment efficacy is relatively sparse due to the exclusion of patients with *EGFR exon20ins* from large EGFR TKI trials. Patients with *EGFR exon20ins* exhibit primary resistance to currently available EGFR TKIs and face poor clinical outcomes.[16,17] A recent retrospective case series study assessing first-line EGFR TKI therapy in patients with *EGFR exon20ins* demonstrated a median OS of 16.8 months,[18] which is approximately half of 31.6 months reported in patients with *cEGFR* treated with afatinib in the LUX-Lung 3 study.[6] In a pooled analysis of the LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6 studies in patients with *EGFR exon20ins*, frontline afatinib resulted in a median OS of 9.2 months and a median PFS of 2.7 months.[19] Treatment with the first-generation EGFR TKIs as second-line therapy has also been shown in a prospective observational study to produce similarly poor outcomes in patients with *EGFR exon20ins*—a median OS of 12.9 months and a median PFS of 1.9 months.[20] Second-line afatinib similarly resulted in a median time to treatment failure of 3.6 months in patients with *EGFR exon20ins*.[21] Real-world data from the US Flatiron electronic health record database showed that second-line treatment in patients with *EGFR exon20ins* was associated with a median PFS of only 3.7 months.[22] However, emergent targeted therapies may improve outcomes in this population. Preliminary data from the *EGFR exon20ins*-specific TKIs, poziotinib and CLN-081, showed overall response rates (ORRs) of 15% and 40%, respectively, in the post-platinum setting.[23,24] Response to standard doses of osimertinib has also been reported, although in a limited number of patients.[25,26] Notably, amivantamab, an EGFR-MET bispecific antibody, which demonstrated an ORR of 40% and a median duration of response of 11.1 months, was recently granted accelerated approval by the US Food and Drug Administration (FDA; May 2021) for adult patients with locally advanced or metastatic NSCLC with *exon20ins* whose disease has progressed on or after platinum-based chemotherapy.[27,28] Mobocertinib, an *EGFR exon20ins*-specific TKI, was also granted US FDA approval for the same patient population.[29]

Patients with *EGFR exon20ins* were often excluded from phase 3 trials of the now-approved EGFR TKIs. As a result, the natural history, treatment patterns, and clinical outcomes in these patients are not well characterized. Furthermore, to our knowledge, outcomes in patients with *EGFR exon20ins* have not been directly compared with those with *cEGFR* in a real-world setting. We undertook this real-word evidence analysis to assess 1) the prognostic value of *EGFR exon20ins* compared with *cEGFR* in patients with advanced NSCLC, 2) the predictive value of EGFR TKI therapy for clinical benefit in *EGFR exon20ins* compared with *cEGFR*, and 3) real-world patient characteristics, treatment patterns, and clinical outcomes of patients with *EGFR exon20ins*.

2. Methods

2.1. Study design and patients

The Flatiron Health database is a nationwide longitudinal, demographically and geographically diverse de-identified database derived from electronic health record (EHR) data from over 280 cancer clinics (~800 sites of care) including more than 2.4 million US cancer patients available for analysis. The de-identified patient-level data in the EHRs include structured data (eg, laboratory values and prescribed drugs) and unstructured data collected via technology-enabled chart abstraction from physician's notes and other unstructured documents (eg, biomarker reports). These data were used to generate an advanced NSCLC-specific, subscription-based real-world dataset that enables researchers to monitor and analyze key aspects of the patient journey. The dataset delivers a wide pool of clinical data, including patient demographics, treatment, and clinical outcomes.

This retrospective cohort study included de-identified adult patients (aged $\geq$ 18 years) of either sex in the advanced NSCLC Flatiron registry EHR database between January 1, 2011 and May 31, 2020. The data were obtained through a license agreement. Other key eligibility criteria were 1) confirmed diagnosis of advanced NSCLC (stage IIIB, IIIC, IVA, or IVB) or early-stage NSCLC with subsequent recurrent or progressive disease, with at least 2 documented clinical visits during the study period, 2) start of first-line therapy within 90 days following advanced NSCLC diagnosis, 3) structured activity (eg, office visit, medication fill) within 90 days following advanced NSCLC diagnosis, and 4) positive test result for *EGFR exon20ins* or *cEGFR* before or up to 28 days after the index date. Patients with both *EGFR exon20ins* and *cEGFR* mutations were excluded.

For the prognostic value analysis, the start date of the first-line treatment was the index date; for the predictive value analysis, the start date of a line of the first EGFR TKI treatment was the index date. Real-world patient characteristics, treatment patterns, and clinical outcomes in patients with *EGFR exon20ins* were evaluated at first-line (treatment naive) and second-line (relapsed/refractory) therapy, and the start date of the first- and second-line treatment, respectively, was the index date. The availability of the patient chart in the EHR for all patients treated in the Flatiron network allowed a longitudinal follow-up of eligible patients. Because only data from de-identified patient health records were used, and no individually identifiable data were collected, used, or transmitted, approval from an Institutional Review Board (IRB) and informed patient consent were not required. Flatiron Health has a master research parent protocol that has been approved by the IRB of record for Flatiron Health, and a waiver has been obtained for informed consent and Health Insurance Portability and Accountability Act authorization based on minimal risk research.

2.2. Study endpoints

Prognostic value is a measurement of the natural history of disease, agnostic of the therapies provided. The prognostic value of *EGFR exon20ins* was assessed by comparing real-world OS (rwOS; primary endpoint) in patients with *EGFR exon20ins* vs *cEGFR*. As part of a sensitivity analysis, rwOS estimates were also examined using the date of advanced diagnosis instead of start date of first-line therapy as index date.

A biomarker is predictive when its presence or absence is correlated with response to a particular treatment. For the purposes of this analysis, predictive value of *EGFR exon20ins* was assessed by comparing real-world PFS (rwPFS; primary endpoint) in patients with *EGFR exon20ins* vs *cEGFR* who received EGFR TKI therapy. To account for any differences in timing of EGFR TKI use in the 2 cohorts, the analysis was stratified by line of therapy when TKI was initiated. Furthermore, the impact of using first-, second-, or third-generation EGFR TKI was evaluated in a sensitivity analysis.

Secondary endpoints were rwPFS and real-world time to next therapy (rwTTNT) for the prognostic value analysis and rwOS and rwTTNT for the predictive value analysis.

2.3. Data conventions and statistical analysis

Real-world OS was defined as the time from index date (start date of first-line therapy) to death. The start date of first-line therapy was chosen instead of date of advanced disease diagnosis because most patients by the start date of first-line therapy have their biomarker tests available, which helps avoid potential bias of immortal time (time from the date of advanced diagnosis to date of biomarker test during which a death event cannot be observed). Due to privacy regulations, only month and year of death were available; therefore, for patients with a month and year of death, 15th day of the month or the day following the last confirmed activity date, whichever was later, was considered the date of death. Patients without a death date were treated as censored at the last confirmed activity date. Real-world PFS was defined as the time from index date (start date of the first EGFR TKI treatment line for the predictive value analysis) to the first episode of disease progression or death; rwTTNT was defined as the time from the index date to the start date of the next line of therapy or death, censoring at the last activity date for patients without a next line of therapy and not known to be dead.

Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA). The endpoints of rwOS, rwPFS, and rwTTNT were summarized using Kaplan–Meier estimates for each cohort, including median and quartiles of survival with 95% CIs. For the prognostic value analysis, adjusted hazard ratio (HR), its 95% CI, and p values were calculated using multivariable Cox proportional hazards model, including the covariates of age, time from diagnosis of advanced disease to treatment, time from initial to advanced diagnosis, line of therapy, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, sex, and practice type (community/academic). For the predictive value analysis, the EGFR TKI line of therapy was used as stratum, in addition to the covariates used in the Cox model for the

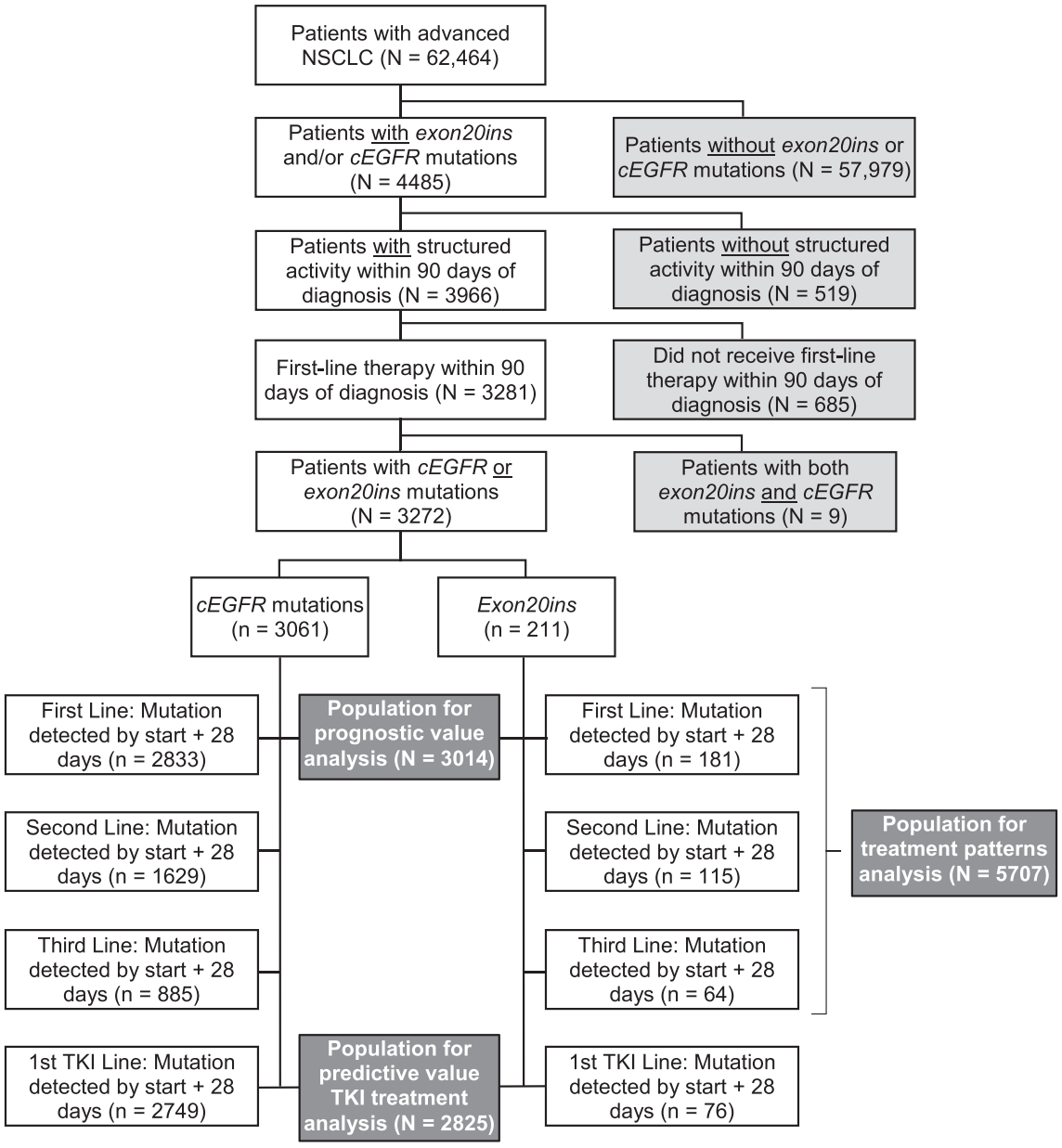

Fig. 1. Patient disposition for treatment lines 1–3 and study populations. *cEGFR*, common *EGFR* mutations; EGFR, epidermal growth factor receptor; *exon20ins*, *EGFR* exon 20 insertions; TKI, tyrosine kinase inhibitor.

prognostic value analysis. Patient characteristics, treatment patterns, and clinical outcomes for patients with *EGFR exon20ins* were reported using descriptive statistics.

From prior experience with the Flatiron database, it was anticipated that ECOG PS would not have been systematically captured for every patient included in this analysis. Covariate adjusted analyses handled missing values in 2 ways. The primary method considered missing values as another category for a categorical covariate. For a sensitivity analysis, missing values of a categorical covariate were imputed with the mode of non-missing values of this covariate. A sensitivity analysis on a subgroup of patients with an index year between 2015 and 2020 was conducted to allow for increasing availability of ECOG PS through this period for both prognostic value and predictive analyses. In addition, *EGFR exon20ins* and *cEGFR* identified at any time were included with delayed entry model (left truncation) as a sensitivity analysis for rwOS.

3. Results

3.1. Patient disposition and baseline characteristics

Among 62,464 patients with advanced NSCLC in the Flatiron registry database, 38,928 had *EGFR* mutations tested, of which 4485 (11.5%) had either *cEGFR* or *EGFR exon20ins*, detected primarily by next-generation sequencing or polymerase chain reaction. Of these, 3272 patients had structured activity (eg, office visit, medication fill) within 90 days following diagnosis, had received first-line therapy within 90 days following diagnosis, and had *cEGFR* (n = 3061 [93.6%]) or *EGFR exon20ins* (n = 211 [6.4%]) (Fig. 1). For prognostic value analysis, 3014 patients (*cEGFR*, 2833; *EGFR exon20ins*, 181) met all study criteria and had an *EGFR* mutation detected before or up to 28 days after the start of treatment; the corresponding numbers were 1744 patients for second-line therapy (*cEGFR*, 1629; *EGFR exon20ins*, 115) and 949 patients for third-line therapy (*cEGFR*, 885; *EGFR exon20ins*, 64). For predictive value analysis, 2825 patients (*cEGFR*, 2749; *EGFR exon20ins*, 76) had an *EGFR* mutation detected before or up to 28 days after the start of first EGFR TKI line of therapy. The demographic and baseline clinical characteristics were generally balanced between the *cEGFR* and *EGFR exon20ins* cohorts in both prognostic and predictive analyses populations (Table 1).

3.2. Prognostic value of EGFR Exon20ins vs cEGFR

Among 3014 patients eligible for prognostic value analysis, 2833 had *cEGFR* and 181 had *exon20ins*. Overall, 114 patients (63.0%) died in the *EGFR exon20ins* cohort compared with 1575 (55.6%) in the *cEGFR* cohort. The median rwOS was 16.2 months (95% CI, 11.04–19.38 months) in the *EGFR exon20ins* cohort compared with 25.5 (24.48–27.04) months in the *cEGFR* cohort (adjusted HR, 1.75 [1.45–2.13]; $p < 0.0001$) (Fig. 2A; Supplementary Table 1). The 5-year rwOS rate was 8% in the *EGFR exon20ins* cohort compared with 19% in the *cEGFR* cohort.

The sensitivity analysis for the primary endpoint rwOS and subgroup analyses are shown in Supplementary Fig. 1. Consistent with the primary analysis, the sensitivity analysis that used ECOG PS ≤ 1 as category for missing ECOG PS and the one that used index year ≥ 2015 showed that patients with *exon20ins* had worse prognosis compared with those with *cEGFR*. The subgroup analyses for missing ECOG PS and ECOG PS ≤ 1 showed similar results. In addition, the sensitivity analysis that calculated rwOS from the date of advanced diagnosis instead of start of first-line therapy resulted in approximately 1-month longer median OS for both cohorts, but the HRs and CIs were similar to those from the primary analysis. The primary analysis excluded 30 patients with *exon20ins* and 228 with *cEGFR* who had their mutation detected more than 28 days after start of first-line therapy. To assess the effect of including these patients on prognostic value of *exon20ins*, a delayed entry Cox proportional hazards model was used; the model showed that including these

Table 1
Demographic and Baseline Clinical Characteristics.

Characteristic	Prognostic Value Analysis		Predictive Value Analysis	
	cEGFR (N = 2833)	*Exon20ins* (N = 181)	*cEGFR* (N = 2749)	*Exon20ins* (N = 76)
Line of EGFR TKI therapy, n (%)				
1	NA	NA	2239 (81.4)	43 (56.6)
2	NA	NA	431 (15.7)	19 (25.0)
≥3	NA	NA	79 (2.9)	14 (18.4)
Age, Mean (SD), years	68.0 (10.7)	66.0 (10.3)	68.0 (10.6)	68.7 (9.0)
Female, n (%)	1895 (66.9)	111 (61.3)	1842 (67.0)	43 (56.6)
Race, n (%)				
White	1603 (56.6)	109 (60.2)	1554 (56.5)	47 (61.8)
Asian	379 (13.4)	11 (6.1)	374 (13.6)	8 (10.5)
Black or African American	205 (7.2)	17 (9.4)	203 (7.4)	5 (6.6)
Hispanic or Latino	6 (0.2)	1 (0.6)	6 (0.2)	1 (1.3)
Other	335 (11.8)	23 (12.7)	317 (11.5)	7 (9.2)
Unknown	305 (10.8)	20 (11.0)	295 (10.7)	8 (10.5)
Ethnicity, n (%)				
Hispanic	146 (5.2)	9 (5.0)	146 (5.3)	4 (5.3)
Unknown	2687 (94.8)	172 (95.0)	2603 (94.7)	72 (94.7)
ECOG PS, n (%)				
≤1	1327 (46.8)	96 (53.0)	1246 (45.3)	33 (43.4)
≥2	292 (10.3)	13 (7.2)	296 (10.8)	8 (10.5)
Unknown	1214 (42.9)	72 (39.8)	1207 (43.9)	35 (46.1)
Histology, n (%)				
Non-squamous	2741 (96.8)	174 (96.1)	2660 (96.8)	76 (100.0)
Squamous	40 (1.4)	5 (2.8)	37 (1.3)	0
NSCLC histology NOS	52 (1.8)	2 (1.1)	52 (1.9)	0
Group stage at initial diagnosis, n (%)				
Stage I	176 (6.2)	12 (6.6)	164 (6.0)	6 (7.9)
Stage II	93 (3.3)	8 (4.4)	86 (3.1)	3 (3.9)
Stage III	178 (6.3)	11 (6.1)	171 (6.2)	5 (6.6)
Stage IIIB/C	103 (3.6)	8 (4.4)	101 (3.7)	2 (2.6)
Stage IV	2229 (78.7)	140 (77.3)	2177 (79.2)	59 (77.6)
Unknown	54 (1.9)	2 (1.1)	50 (1.8)	1 (1.3)
Smoking history, n (%)				
Yes	1271 (44.9)	97 (53.6)	1220 (44.4)	37 (48.7)
No	1550 (54.7)	84 (46.4)	1518 (55.2)	39 (51.3)
Unknown	12 (0.4)	0	11 (0.4)	0
Practice type, n (%)				
Community	2532 (89.4)	161 (89.0)	2445 (88.9)	67 (88.2)
Academic	301 (10.6)	20 (11.0)	304 (11.1)	9 (11.8)
Time from advanced diagnosis to treatment, mean (SD), months	1.1 (0.65)	1.1 (0.62)	2.6 (5.52)	7.0 (10.25)
Time from initial to advanced diagnosis, mean (SD), months	4.9 (15.24)	6.6 (19.45)	4.7 (14.86)	6.5 (18.01)

cEGFR, common *EGFR* mutations; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; *exon20ins*, *EGFR* exon 20 insertions; NA, not applicable.

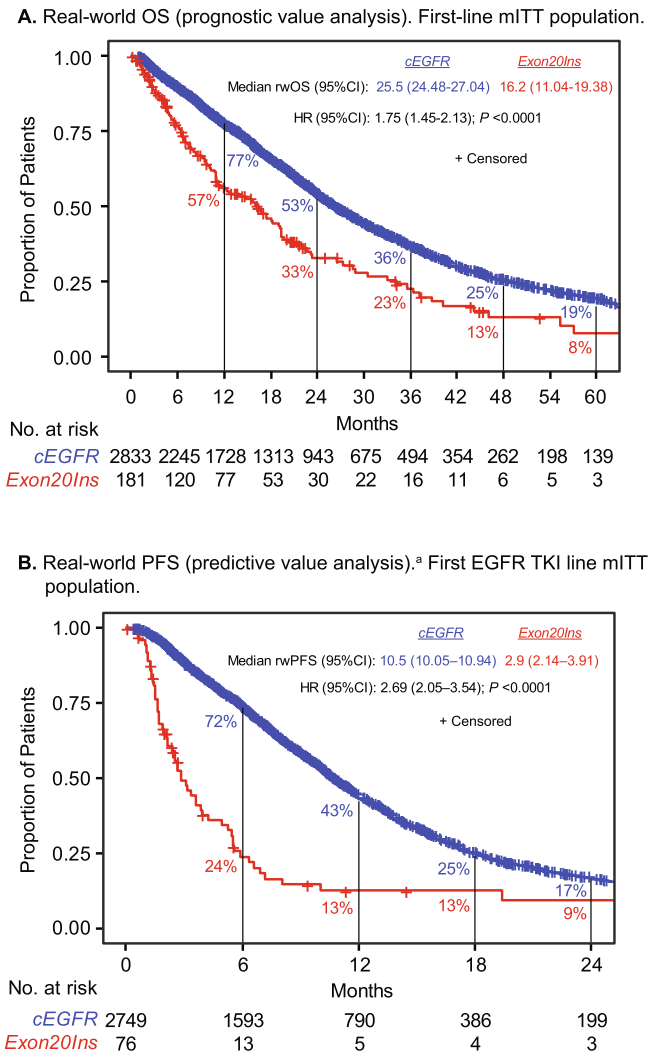

Fig. 2. rwOS and rwPFS (primary endpoints) estimated by Kaplan-Meier curves in patients with *EGFR exon20ins* (red) vs *cEGFR* (blue). Patients with positive test results for *EGFR exon20ins* or *cEGFR* before or up to 28 days after the index date were included. HR, hazard ratio; *cEGFR*, common *EGFR* mutations; EGFR, epidermal growth factor receptor; *exon20ins*, *EGFR* exon 20 insertions; mITT, modified intent-to-treat; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; TKI, tyrosine kinase inhibitor. [a]Analysis stratified by line of treatment. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

patients did not change the HRs and CIs from the primary analysis. The low number of patients with ECOG PS ≥ 2 in the *EGFR exon20ins* cohort made the HR estimate unreliable and resulted in a wide CI.

In patients with *EGFR exon20ins* vs *cEGFR* receiving any first-line therapy, the secondary endpoints of rwPFS and rwTTNT showed similar results (Supplementary Table 1). The median rwPFS in the *EGFR exon20ins* cohort (5.1 [3.71–6.28] months) was significantly shorter compared with that in the *cEGFR* cohort (10.3 [9.92–10.68] months) (adjusted HR, 1.93 [1.61–2.31]; $p < 0.0001$). Similarly, the median rwTTNT in the *EGFR exon20ins* cohort (6.4 [5.22–8.11]) was significantly shorter compared with that in the *cEGFR* cohort (10.8 [10.35–11.30]) (adjusted HR, 1.6 [1.36–1.9]; $p < 0.0001$).

Approximately half of the patients in both the *cEGFR* and *EGFR exon20ins* cohorts received first-generation EGFR TKIs erlotinib or gefitinib as their first EGFR TKI treatment (Table 2). There were no major imbalances in the distribution of EGFR TKI generations across the comparator populations. Approximately 20% to 30% of patients in both cohorts received osimertinib.

Table 2
Summary of First EGFR TKI Use (TKI Generation and Setting)

Parameter	*cEGFR*	*Exon20ins*
First EGFR TKI use (any line), n (%)	N = 2749	N = 76
Gen 1: Erlotinib or Gefitinib	1515 (55.1)	38 (50.0)
Gen 2: Afatinib or Dacomitinib	418 (15.2)	20 (26.3)
Gen 3: Osimertinib	815 (29.6)	18 (23.7)
EGFR TKI on first line, n (%)	N = 2238	N = 43
Gen 1: Erlotinib or Gefitinib	1243 (55.5)	25 (58.1)
Gen 2: Afatinib or Dacomitinib	331 (14.8)	9 (20.9)
Gen 3: Osimertinib	664 (29.7)	9 (20.9)
EGFR TKI on second line, n (%)	N = 1134	N = 25
Gen 1: Erlotinib or Gefitinib	377 (33.2)	11 (44.0)
Gen 2: Afatinib or Dacomitinib	252 (22.2)	7 (28.0)
Gen 3: Osimertinib	505 (44.5)	7 (28.0)
EGFR TKI on third line, n (%)	N = 412	N = 7
Gen 1: Erlotinib or Gefitinib	131 (31.8)	2 (28.6)
Gen 2: Afatinib or Dacomitinib	78 (18.9)	1 (14.3)
Gen 3: Osimertinib	203 (49.3)	4 (57.1)

cEGFR, common *EGFR* mutations; EGFR, epidermal growth factor receptor; *exon20ins*, *EGFR* exon 20 insertions; Gen, generation; TKI, tyrosine kinase inhibitor.

3.3. Predictive value of EGFR TKI treatment for EGFR Exon20ins vs cEGFR

The predictive value analysis compared outcomes on the first use of an EGFR TKI line between patients with *cEGFR* (n = 2749) or *EGFR exon20ins* (n = 76). After a median follow-up period of 20.6 months, 59 events (77.6%) of disease progression or deaths occurred in the *EGFR exon20ins* cohort and 1793 (65.2%) in the *cEGFR* cohort. The median rwPFS estimate (primary endpoint) was 2.9 months (95% CI, 2.14–3.91 months) in the *EGFR exon20ins* cohort compared with 10.5 (10.05–10.94) months in *cEGFR* cohort (adjusted HR, 2.69 [2.05–3.54]; $p < 0.0001$) (Fig. 2B; Supplementary Table 2). The 1-year rwPFS rate was 13% in the *EGFR exon20ins* cohort compared with 43% in the *cEGFR* cohort.

Among patients on the first EGFR TKI line, the median rwOS (secondary endpoint) in the *EGFR exon20ins* cohort (7.5 [5.45–13.34] months) was significantly shorter compared with that in the *cEGFR* cohort (25.5 [24.28–26.81] months) (adjusted HR, 2.70 [2.04–3.57]; $p < 0.0001$; Supplementary Table 2). Similarly, the median rwTTNT (secondary endpoint) was significantly shorter in the *EGFR exon20ins* cohort (3.9 [2.86–5.45] months) compared with that in the *cEGFR* cohort (12.7 [12.29–13.34] months) (adjusted HR, 2.54 [1.97–3.27]; $p < 0.0001$). The predictive value analysis by first-, second-, and third-generation EGFR TKI as first TKI line is presented in Supplementary Table 3.

The sensitivity analysis for the primary endpoint rwPFS and subgroup analyses are shown in Supplementary Fig. 2. Consistent with the primary analysis, the sensitivity analysis that used using ECOG PS ≤ 1 as category for missing ECOG PS and the one that used index year ≥ 2015 subset showed that when treated with EGFR TKIs, patients with *exon20ins* had worse outcomes compared with those with *cEGFR*. The subgroup analyses for missing ECOG PS and ECOG PS ≤ 1 showed similar results. In addition, including another covariate—TKI generation—to the primary analysis produced HRs and CIs that were approximately the same as those for the primary analysis. The low number of patients with ECOG PS ≥ 2 in the *EGFR exon20ins* cohort made the HR estimate unreliable and resulted in a wide CI.

3.4. Treatment patterns in patients with EGFR Exon20ins

Most patients (61.3%) with *EGFR exon20ins* were prescribed platinum-based chemotherapy regimens in the first-line setting, followed by EGFR TKI monotherapy (21.5%) (Table 3). It is noteworthy

Table 3
Treatment Patterns in Patients With *EGFR* Exon 20 insertions.

Treatment, n (%)	First Line (N = 181)	Second Line (N = 115)	Third Line (N = 64)
Platinum based regimen	111 (61.3)	27 (23.5)	14 (21.9)
Platinum doublet	50 (27.6)	13 (11.3)	5 (7.8)
Platinum + EGFR TKI	1 (0.6)	0	0
Platinum + immunotherapy	32 (17.7)	8 (7.0)	2 (3.1)
Platinum + EGFR TKI + immunotherapy	1 (0.6)	0	0
Platinum + EGFR TKI + VEGFi	1 (0.6)	0	0
Platinum + immunotherapy + VEGFi	1 (0.6)	0	0
Platinum + VEGFi	25 (13.8)	5 (4.3)	7 (10.9)
Platinum alone	0	1 (0.9)	0
EGFR TKI alone	39 (21.5)	25 (21.7)	7 (10.9)
EGFR TKI Combinations	1 (0.6)	0	0
Immunotherapy alone	16 (8.8)	33 (28.7)	14 (21.9)
VEGFi alone	1 (0.6)	11 (9.6)	7 (10.9)
Non-platinum chemotherapy	5 (2.8)	15 (13.0)	19 (29.7)
Others	8 (4.4)	4 (3.5)	3 (4.7)

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; VEGFi, vascular endothelial growth factor inhibitor.

that 21.5% of patients did receive first-line EGFR TKIs. In the second- and third-line setting, several different therapies were used, including immunotherapy, EGFR TKI monotherapy, platinum-based regimens, and non-platinum chemotherapy. The treatment patterns in patients with *cEGFR* are shown in Supplementary Table 4.

3.5. Clinical outcomes by therapy type in first and second lines in patients with EGFR Exon20ins

Survival outcomes (rwOS and rwPFS) were assessed in patients with *EGFR exon20ins* receiving different therapies in first and second lines. Across all therapies in the frontline setting, the median rwOS was 16.2 months, and the median PFS was 5.1 months (Fig. 3). In the second-line setting across all therapies, the median rwOS was 13.3 months, and the median PFS was 3.2 months. Platinum-based chemotherapy was associated with the longest median rwOS (first line, 17.4 months; second line, 14.2 months) and rwPFS (6.6 and 5.0 months, respectively). The survival outcomes in the second-line setting were heterogeneous across treatments and generally poor; the median rwPFS estimates were notably poor, ranging from 2.3 to 5.2 months.

4. Discussion

In this retrospective real-world cohort study, we found that patients with NSCLC harboring *EGFR exon20ins* had a significantly worse prognosis compared with those having *cEGFR* mutations. Across all frontline treatments, the risk of death was 75% higher (adjusted HR, 1.75; see Fig. 2A and Supplementary Table 1) and the risk of disease progression or death was 93% higher (adjusted HR, 1.93; see Supplementary Table 1) in patients with *EGFR exon20ins* vs *cEGFR*. Similarly, the predictive value analysis showed that after initiating EGFR TKI treatment, patients with *EGFR exon20ins* experienced significantly inferior outcomes compared with those with *cEGFR*; the risk of progression or death increased by 169% (adjusted HR, 2.69; see Fig. 2B and Supplementary Table 2) and that of death increased by 170% (adjusted HR, 2.70; see

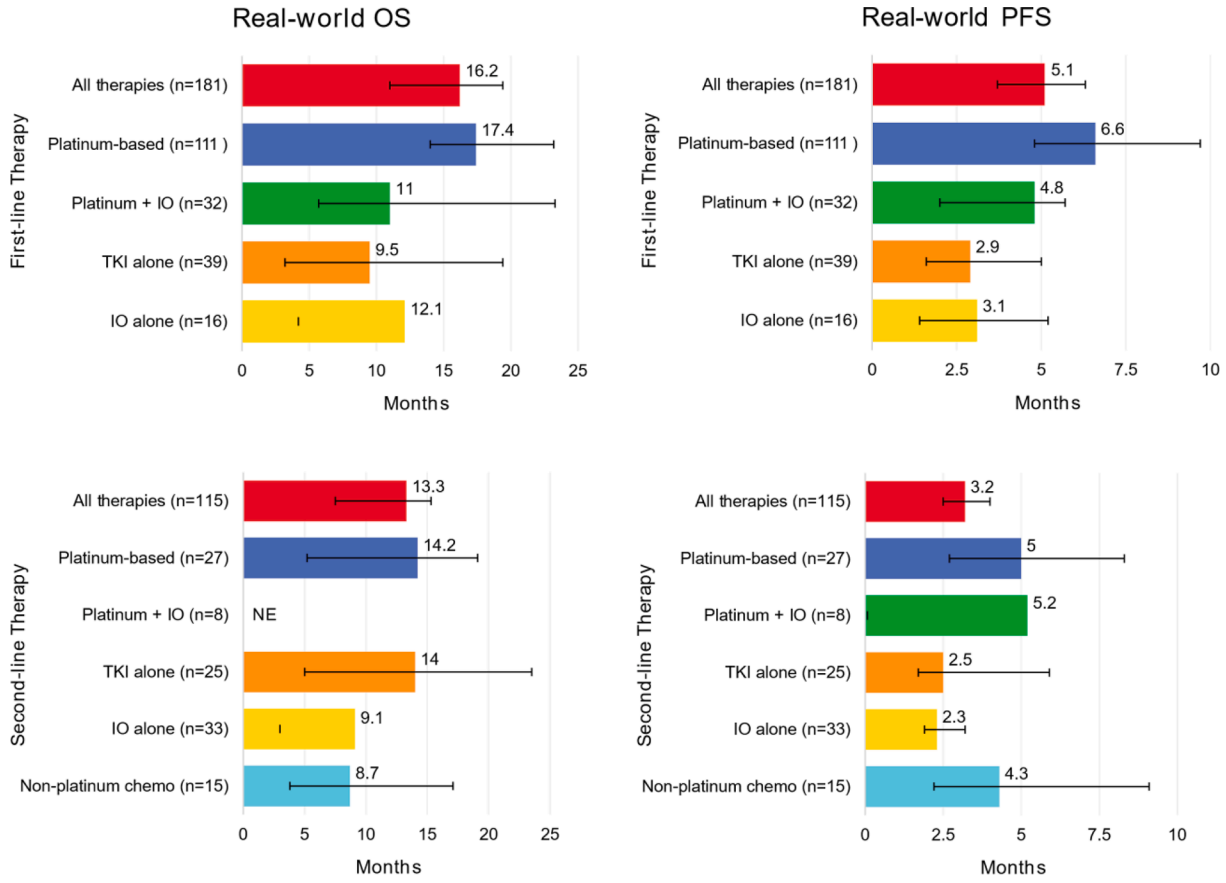

Fig. 3. Clinical outcomes (median ± 95% CI) by therapy type in first and second lines in patients with *EGFR exon20ins*. The IO alone real-world OS data (first- and second-line therapy) and platinum + IO real-world PFS data (second-line therapy) did not have the upper bound of its 95% CI. EGFR, epidermal growth factor receptor; *exon20ins*, *EGFR* exon 20 insertions; IO, immunotherapy; NE, not estimable; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

Supplementary Table 2). Our findings are consistent with other real-world studies showing poor outcomes for patients with *EGFR exon20ins*.[22,30,31]

Assessment of treatment patterns demonstrated heterogeneity in second-line treatments, with poor outcomes across all treatments, especially rwPFS (average across treatments was 3.2 months). Despite the known lack of efficacy of EGFR TKI in patients with *EGFR exon20ins* NSCLC, TKI monotherapy was given in the frontline setting in 21.5% of patients in the real-world setting.

The rwPFS and rwOS outcomes with EGFR TKI therapy in patients with *cEGFR* in the present study are consistent with those from phase 3 trials assessing outcomes with first- and second-generation EGFR TKIs,[3–6,10–12] which were the predominant EGFR TKIs utilized in this database. Third-generation EGFR TKIs (eg, osimertinib) were developed to target the *EGFR* T790M mutation that is responsible for acquired resistance to first- and second-generation EGFR TKIs.[32] First-line treatment with osimertinib has shown improved median OS compared with first-generation EGFR TKIs (38.6 vs 31.8 months) in patients with *cEGFR* mutations.[14] Frontline use of osimertinib was approved for the treatment of NSCLC with *cEGFR* in April 2018,[33] indicating that most patients in the present study, which included data from 2011 through May 2020, were unlikely to have received this drug. However, 20% to 30% of patients in the present study did receive osimertinib, suggesting its prevalent use post approval and that the difference in outcomes between *EGFR exon20ins* and *cEGFR* cohorts observed here could further increase as osimertinib continues to be prescribed in the first-line setting to patients with *cEGFR*.

Analyses involving EHR data, such as the Flatiron database, are associated with certain limitations. Flatiron data are generated from real-world clinical practice settings and, therefore, are subject to missing data or data entry errors. In addition, information about treatment outside of the specific cancer care sites may not have been captured. Similarly, information about patients prior to the adoption of EHRs may not have been included. Treatment regimens for the patients included in this database were determined by physicians' discretion based on many confounding factors that may be unaccounted for, limiting the interpretability of the predictive analysis. Ultimately, *exon20ins* are highly diverse, which may bring heterogeneity in the efficacy of available options; one example is the FQEA insertions that may predict response to EGFR TKIs.[34,35]

Generalizability of the analysis is limited by multiple factors. For example, the advanced NSCLC Flatiron registry database mostly includes patients treated at community oncology clinics, and patients not seeking systemic treatment or treated outside the Flatiron network could have different outcomes. Informative censoring (eg, sicker patients leaving the database and potentially missing death data) may bias estimates of survival, limiting ability to compare OS estimates with those from other data sources. One covariate—ECOG PS—had a large amount of missingness (40%-46%) in this study, which could have introduced bias; however, the rate of missingness was similar between the 2 cohorts. It was assumed that the missingness of ECOG PS was random. Furthermore, the sensitivity analyses that used ECOG PS ≤ 1 for missing ECOG PS produced results that were consistent with primary analyses.

In conclusion, the results of this retrospective real-world cohort study show that patients with *EGFR exon20ins* have poorer prognosis than those with *cEGFR*, with 5-year rwOS of 8% and 19%, respectively. Patients with *EGFR exon20ins* receive little benefit from EGFR TKI treatment, have no standard of care in the second-line setting, and are in urgent need of new treatment options. Two new therapies, amivantamab—a bispecific antibody against EGFR and MET receptor—and mobocertinib—an *EGFR exon20ins*-specific TKI—both recently received accelerated approval for adult patients with locally advanced or metastatic NSCLC with *EGFR exon20ins* whose disease has progressed on or after platinum-based chemotherapy.[27,29]

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

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