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Nicolas Girard,[1] Anna Minchom,[2] Sai-Hong Ignatius Ou,[3] Shirish M. Gadgeel,[4] José Trigo,[5] Santiago Viteri,[6] Joshua M. Bauml,[7,#] Anil Londhe,[8] Parthiv Mahadevia,[8] Lyudmila Bazhenova[9]

Abstract

The activity of immune checkpoint inhibitors (ICIs) in NSCLC harboring EGFR exon 20 insertion mutations (ex20ins) has not been extensively studied. In this real-world analysis, patients with EGFR ex20ins NSCLC had shorter median time to next therapy after first ICI treatment than patients with wildtype NSCLC, suggesting that ICIs may not be effective in EGFR ex20ins NSCLC.

Introduction: The activity of immune checkpoint inhibitors (ICIs) in NSCLC harboring EGFR exon 20 insertion mutations (ex20ins) has not been closely examined due to the frequent exclusion of patients with EGFR mutations from large immunotherapy-based NSCLC trials. **Patients and Methods:** A real-world, retrospective study was conducted to compare outcomes of ICI-treated patients with EGFR ex20ins and wildtype NSCLC (wt-NSCLC; defined as EGFR and ALK test negative). Patients with advanced NSCLC from the Flatiron Health database (2015-2020) were included in the analysis. Real-world time to next therapy (rwTTNT) and overall survival (rwOS), stratified by ICI initiation line of therapy, were the prespecified primary and secondary endpoints, respectively. **Results:** Among 59 patients with EGFR ex20ins NSCLC and 5365 with wt-NSCLC, ICI treatment was received as first-line therapy in 25% and 39%, respectively. Patients with EGFR ex20ins had a 58% increased risk of shorter time to next-line therapy compared with wt-NSCLC (adjusted hazard ratio of 1.58 [95% confidence interval [CI], 1.2-2.1]; $P = .0012$). The median rwTTNT for first ICI line was 3.7 months (95% CI, 3.0-4.9) for EGFR ex20ins NSCLC compared with 5.8 months (95% CI, 5.6-6.0) for wt-NSCLC. No meaningful difference in rwOS between the groups was observed. **Conclusions:** ICI therapy may be less effective for patients with EGFR ex20ins compared with wt-NSCLC. Consistent with prior data on exon 19 deletion and L858R substitution, tumors harboring ex20ins appear to be less responsive to immune checkpoint inhibition than wt-NSCLC.

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Keywords: Immunotherapy, Mutation, Real-world data, Real-world overall survival, Time to next treatment

Introduction

Treatment with immune checkpoint inhibitors (ICIs) have led to longer remissions and overall survival in patients with NSCLC, with 5-year survival rates of approximately 15% to 30% in advanced disease, as second- and first-line treatment, respectively.[1,2] However, not all patients will respond to ICIs due to primary or acquired resistance.[3]

Abbreviations: ALK, anaplastic lymphoma kinase; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ex20ins, exon 20 insertion mutations; HR, hazard ratio; ICI, immune checkpoint inhibitor; PD-L1, programmed death-ligand 1; rwOS, real-world overall survival; rwTTNT, real-world time to next treatment; TKI, tyrosine kinase inhibitor; wt, wildtype.

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Exon 20 insertion mutations (ex20ins) are the third most frequent mutation in EGFR-mutant NSCLC, accounting for up to 12% of cases.[4-6] While it is known that patients who harbor these mutations are generally insensitive to tyrosine kinase inhibitors (TKIs), less is known about the activity of ICIs in this population, as many large immunotherapy-based trials have excluded patients with any type of EGFR mutations.[7] It is recognized that ICIs are not very effective in patients with exon 19 deletion and L858R EGFR mutation-positive NSCLC,[8-12] but the activity of ICIs in patients with EGFR ex20ins NSCLC has been inconclusive given the scarcity of data in this patient population.[8,13-15] In retrospective analyses using institutional databases, reported response to ICI therapy has ranged from 6.7% (1 response in 15 patients)[15] to 50% (3 responses in 6 patients).[14] In another retrospective institutional study with a larger population of 28 patients with EGFR ex20ins NSCLC, an overall response rate of 10.7% was reported.[8]

Given the limited and varying data on ICI therapy in the literature, we conducted a retrospective study using real-world data to compare clinical outcomes in patients with EGFR ex20ins and wildtype NSCLC (wt-NSCLC; defined as EGFR and ALK test negative) treated with ICI therapy.

Patients and Methods

Study Design

The study included deidentified patients aged ≥ 18 years with a diagnosis of advanced NSCLC between January 1, 2011 and December 31, 2020 from the Advanced NSCLC Flatiron Registry electronic health record-derived database (Flatiron Health, Inc., New York, NY). Eligible patients had ≥ 2 documented clinical visits on or after January 1, 2011, structured activity (eg, office visit, medication fill), initiated first-line therapy within 90 days of diagnosis, and a positive test result (EGFR ex20ins) or negative test results (EGFR and ALK for wt-NSCLC) prior to or within 28 days of start of line of therapy. The study objectives were to evaluate the predictive value of EGFR ex20ins vs. wt-NSCLC to first ICI treatment (at any line of therapy, excluding ICI received in combination with any other therapies) and to determine real-world patient characteristics, treatment patterns, and clinical outcomes of both groups in patients with index date of 2015 or later to reflect availability of ICIs for the treatment of NSCLC. Subsequent, exploratory analysis of the subset of patients who received first-line ICI-chemotherapy was performed. The primary endpoint was real-world time to next treatment (rwTTNT), and real-world overall survival (rwOS) was the secondary endpoint.

Data were obtained from deidentified patient health records, with no identifiable data collected, used, or transmitted; therefore, approval from an Institutional Review Board (IRB) and informed patient consent were not required. A master research parent protocol 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. Data from Flatiron were used under license for the current study and are not publicly available. Other researchers should contact Flatiron Health, Inc.

Statistical Analyses

rwTTNT was defined as the time from the first ICI line to the start date of the next line of therapy or death; patients without a next line were censored at the last activity date. rwOS was defined as the time from the first ICI line to death; patients without a date of death were censored at the last confirmed activity date.

The endpoints of rwTTNT and rwOS were summarized using the Kaplan-Meier method, including median and 95% confidence intervals (CIs) for each group. To assess the predictive value of EGFR ex20ins compared with wt-NSCLC to ICI treatment, adjusted hazard ratios (HRs) and its 95% CI and *P*-value were calculated using multivariate Cox proportional hazard models stratified by ICI initiation line of therapy, with covariates of age, time from advanced diagnosis to index date, time from initial to advanced diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS), smoking history, sex, and practice type. Patient characteristics, treatment patterns, and clinical outcomes were reported using descriptive statistics. Statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC).

Results

Patients and Real-World Treatment Patterns

Among 67,281 patients with advanced NSCLC, 192 had EGFR ex20ins NSCLC and 16,786 had wt-NSCLC (Figure 1). In both the EGFR ex20ins and wt-NSCLC groups, platinum-based regimens (excluding platinum chemotherapy + ICI) were the most frequent first-line therapy (38.8% and 45.3%, respectively) and ICIs were the most frequent second-line therapy (27.8% and 41.2%, respectively; Figure 2). First-line platinum chemotherapy in combination with an ICI was received by 20.9% of the EGFR ex20ins and 26.0% of the wt-NSCLC group.

Predictive Value of ex20ins vs. wt-NSCLC to ICI Treatment

Clinical outcomes to ICI therapy were assessed in 59 patients with EGFR ex20ins NSCLC and 5365 with wt-NSCLC (Figure 1). The demographic and baseline clinical characteristics were generally similar between both groups, with the exceptions of smoking history and median time from advanced diagnosis to treatment (Table 1). As expected for EGFR ex20ins NSCLC, a larger proportion of patients were nonsmokers compared with wt-NSCLC.[7]

The majority of ICI therapy was given in the first or second line in both the EGFR ex20ins (25% and 41%, respectively) and wt-NSCLC (39% and 42%) groups (Table 1). Of the ICI therapies received, nivolumab and pembrolizumab were most common in patients with EGFR ex20ins (64.4% and 32.2%, respectively) and wt-NSCLC (50.6% and 41.5%). Durvalumab (3.4%) was the only other ICI received by patients with EGFR ex20ins NSCLC. Patients with wt-NSCLC also received atezolizumab (4.6%), ipilimumab and nivolumab (1.6%), durvalumab (1.5%), or other therapy (0.02%).

For the primary endpoint of rwTTNT for first ICI line, the median was 3.7 months (95% CI, 3.0-4.9) for the EGFR ex20ins group and 5.8 months (95% CI, 5.6-6.0) for the wt-NSCLC group (Figure 3A). Patients with EGFR ex20ins NSCLC had a 58% increased risk of shorter time to next-line therapy compared with

Figure 1 Patient Selection from the Flatiron Database (2015-2020). ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; ex20ins = exon 20 insertion mutations; ICI = immune checkpoint inhibitor; NSCLC = non-small cell lung cancer; wt = wildtype. [a]Includes 20,711 patients who did not have EGFR, ALK testing performed. [b]Defined as EGFR and ALK test negative. [c]To be eligible, diagnostic testing must have been performed prior to or within 28 days of start of line.

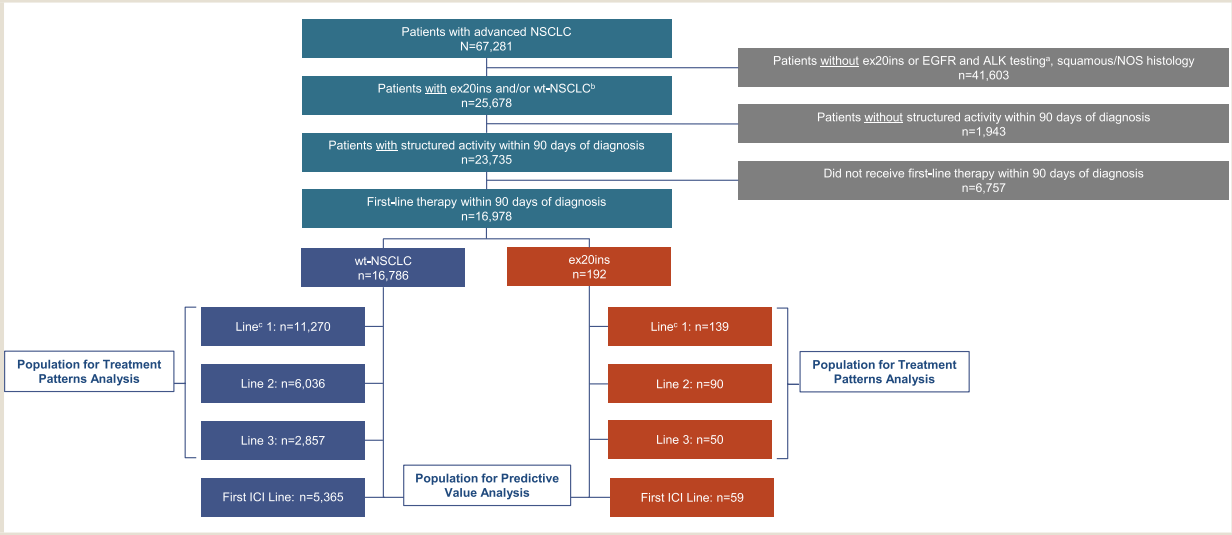
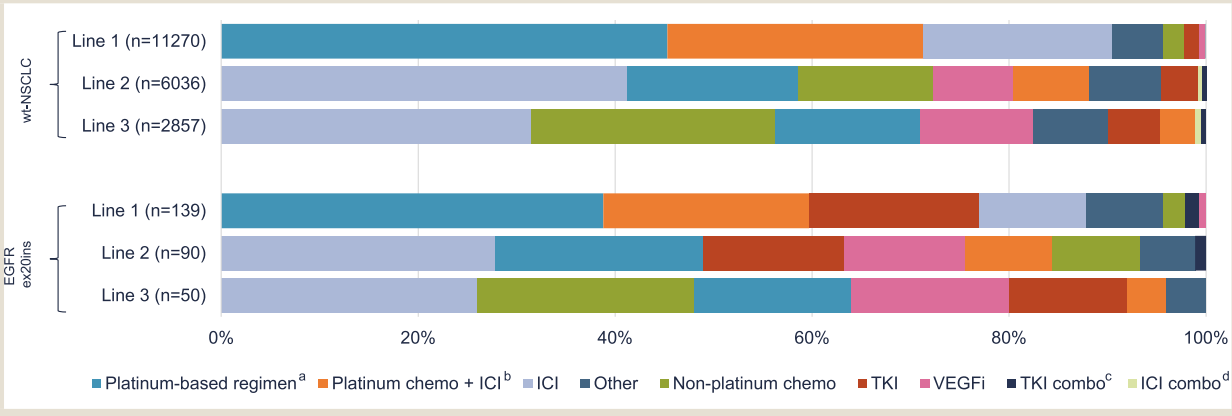


Figure 2 Real-world treatment patterns by line of therapy. Chemo = chemotherapy; combo = combination; EGFR = epidermal growth factor receptor; ex20ins = exon 20 insertion mutations; ICI = immune checkpoint inhibitor; NSCLC = non-small cell lung cancer; Pt = platinum; TKI = tyrosine kinase inhibitor; VEGFi = vascular endothelial growth factor inhibitor; wt = wildtype. Note: TKI therapy included erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib. [a]Pt doublet, Pt + TKI, Pt + ICI + TKI, Pt + ICI + TKI + VEGFi, Pt + TKI + VEGFi, Pt + ICI + VEGFi, Pt + VEGFi, Pt alone. [b]Pt + ICI. [c]TKI + ICI and TKI + VEGFi. [d]ICI + VEGFi.



patients with wt-NSCLC (adjusted HR of 1.58 [95% CI, 1.2-2.1]; $P = .0012$). At the 12-months landmark, only 10% of patients with EGFR ex20ins NSCLC remained on ICI therapy compared with 31% of patients with wt-NSCLC.

For the secondary endpoint of rwOS, no meaningful difference in survival was observed between the EGFR ex20ins and wt-NSCLC groups receiving ICI therapy. The median rwOS was 10.9 months (95% CI, 5.2-14.3) for the EGFR ex20ins group and 11.3 months (95% CI, 10.7-12.0) for the wt-NSCLC group, with an adjusted HR of 1.21 (95% CI, 0.9-1.6) and a *P*-value of .214 (Figure 3B).

Further analysis of EGFR ex20ins vs. wt-NSCLC for those who received first-line ICI-chemotherapy was performed due to this regimen becoming more widely used in NSCLC. Of the 29 patients with EGFR ex20ins and 2934 patients with wt-NSCLC, median TTNT was 8.1 months (95% CI, 5.6-11.0) and 8.0 months (95% CI, 7.5-8.4), respectively, with an HR of 1.03 (95% CI, 0.7-

Table 1 Demographic and Baseline Clinical Characteristics

	wt-NSCLC N = 5365	EGFR Ex20ins N = 59	All N = 5424
Median age (range), years	70 (21-85)	70 (45-85)	70 (21-85)
Sex, n (%)			
Female	2809 (52.4)	32 (54.2)	2841 (52.4)
Male	2555 (47.6)	27 (45.8)	2582 (47.6)
Race, n (%)			
White	3852 (71.8)	37 (62.7)	3889 (71.7)
Other race	532 (9.9)	11 (18.6)	543 (10.0)
Black	440 (8.2)	4 (6.8)	444 (8.2)
Asian	91 (1.7)	4 (6.8)	95 (1.8)
ECOG PS (%)			
≤ 1	2846 (53.0)	30 (50.8)	2876 (53.0)
≥ 2	1078 (20.1)	8 (13.6)	1086 (20.0)
Unknown	1441 (26.9)	21 (35.6)	1462 (27.0)
Smoking history, n (%)			
Yes	4787 (89.2)	31 (52.5)	4818 (88.8)
No	575 (10.7)	28 (47.5)	603 (11.1)
Unknown	3 (0.1)	0	3 (0.1)
Practice type, n (%)			
Academic	359 (6.7)	7 (11.9)	366 (6.7)
Community	5006 (93.3)	52 (88.1)	5058 (93.3)
Median time from advanced diagnosis to treatment (range), months	4.6 (0–103)	8.2 (0–62)	4.6 (0-103)
Median time from initial diagnosis to advanced diagnosis (range), months	0 (0–191)	0 (0–193)	0 (0-193)
First ICI use by line of therapy, n (%)			
1	2114 (39.4)	15 (25.4)	2129 (39.3)
2	2248 (41.9)	24 (40.7)	2272 (41.9)
3	697 (13.0)	13 (22.0)	710 (13.1)
4	192 (3.6)	5 (8.5)	197 (3.6)
5	65 (1.2)	1 (1.7)	66 (1.2)
6	29 (0.5)	0	29 (0.5)
7	13 (0.2)	1 (1.7)	14 (0.3)
≥ 8	7 (0.1)	0	7 (0.1)
ICI therapy received, n (%)			
Nivolumab	2717 (50.6)	38 (64.4)	2755 (50.8)
Pembrolizumab	2227 (41.5)	19 (32.2)	2246 (41.4)
Atezolizumab	249 (4.6)	0	249 (4.6)
Ipilimumab, Nivolumab	88 (1.6)	0	88 (1.6)
Durvalumab	83 (1.5)	2 (3.4)	85 (1.6)
Other	1 (<0.1)	0	1 (<0.1)
PD-L1 status, n (%)			
Available	1465 (27.3)	12 (20.3)	1477 (27.2)
Unavailable	3900 (72.7)	4 (6.8)	3904 (72.0)

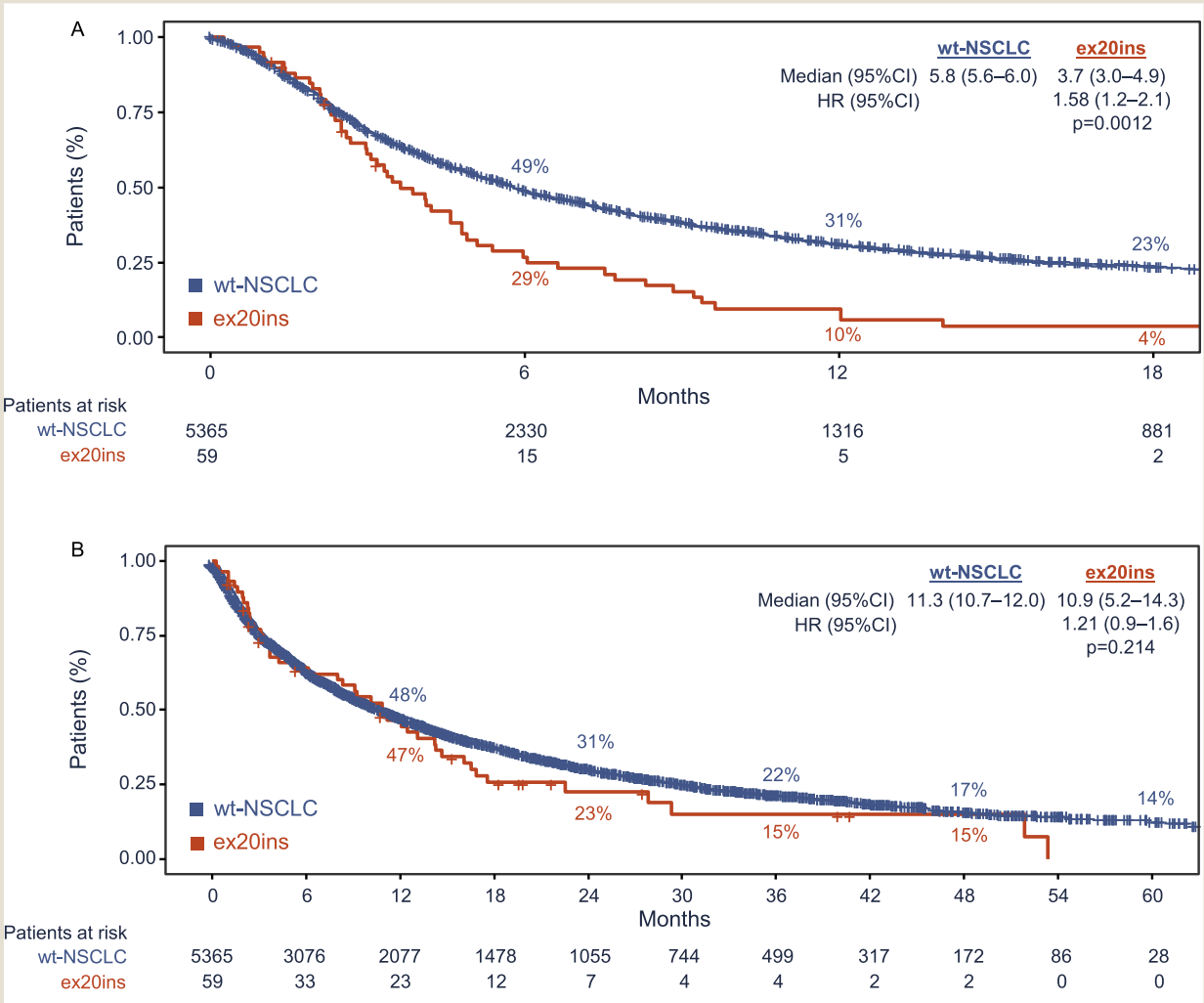
ECOG PS = Eastern Cooperative Oncology Group performance status; EGFR = epidermal growth factor receptor; ex20ins = exon 20 insertion mutations; ICI = immune checkpoint inhibitor; NSCLC = non-small cell lung cancer; PD-L1 = programmed death-ligand 1; wt = wildtype.

1.6; $P = .901$). Median OS was 15.7 months (95% CI, 8.4-23.3) for the EGFR ex20ins group and 12.5 months (95% CI, 11.7-13.4) for the wt-NSCLC group with an HR of 1.01 (95% CI, 0.6-1.7; $P = .966$). No meaningful differences in overall survival or TTNT were observed between the EGFR ex20ins and wt-NSCLC groups receiving first-line ICI-chemotherapy.

Discussion

In this retrospective study, we examined the real-world treatment patterns and the clinical outcomes to ICI therapy in patients with EGFR ex20ins and wt-NSCLC. Treatment patterns were generally similar between the groups, with the majority of patients

Figure 3 Kaplan-Meier curves for real-world (A) Time to Next Treatment and (B) Overall Survival from First ICI Line of Therapy. Hash marks indicate censored patients. EGFR = epidermal growth factor receptor; ex20ins = exon 20 insertion mutations; HR = hazard ratio; ICI = immune checkpoint inhibitor; NSCLC = non-small cell lung cancer; wt, wildtype.



receiving platinum-based chemotherapy regimens and ICIs as first- and second-line treatments. Although no targeted therapies were approved for EGFR ex20ins NSCLC during the time span in this analysis (2015-2020), a considerable proportion of patients were treated with TKIs (17.3% and 14.4%) and ICIs (10.8% and 27.8%) as first- and second-line treatments, respectively.

ICI therapy was less effective for patients with EGFR ex20ins NSCLC, with a 58% increased risk of shorter time to next-line therapy, as compared with patients with wt-NSCLC. This finding is consistent with previous reports of poor outcomes with ICIs in patients with EGFR-mutant NSCLC. Response rates to ICI therapy among patients with EGFR ex20ins NSCLC vary widely, with reported rates between 6.7% and 50.0%; response rates in the higher end of the range were observed in studies with a small number of patients (n = 6 to n = 9).[8,13-15] In the Memorial Sloan Kettering (MSK)-IMPACT study, which examined outcomes to ICI therapy in patients under care at the institution, no difference in the median time to treatment discontinuation was observed between patients with EGFR ex20ins NSCLC (2.8 months) and patients without a targetable alteration (2.8 months), although survival in the EGFR ex20ins group was poorer.[16] rwTTNT in the wt-NSCLC group (5.8 months) was perhaps shorter than expected given data from the KEYNOTE-024 study, which reported a median progression-free survival of 10.3 months with pembrolizumab.[17] However, for patients in our real-world analysis, programmed death-ligand 1 (PD-L1) status was largely unknown, and patients could have received first ICI therapy at any line of treatment whereas those in the KEYNOTE-024 study had ≥ 50% PD-L1 expression and received pembrolizumab only in the front line setting. Additionally, in a meta-analysis of ICI use in NSCLC, the progression-free survival HR was 0.67 (95% CI, 0.5-0.8; P =.0005) for first-line, 0.73 (95% CI, 0.5-1.0; P =.05) for second-line, and 1.70

(95% CI, 1.0-2.9; P =.05) for third-line therapy.[18] Therefore, the survival benefit of immunotherapy was only observed with first- and second-line therapy and does not vary greatly between lines of therapy.

As this was a real-world study using electronic heath record data, missing data and data collection errors are limitations of the analyses. Also, the treatment regimens and the lines with which those treatments are used were determined by physicians' discretion, which may be based on confounding factors that have not been accounted for. In this study, ECOG PS and PD-L1 status were unknown for a large proportion of patients, which may also lead to potential bias. However, as noted in the literature, patients with driver mutations (EGFR mutations, ALK rearrangements) have lower response rates to PD-L1 and PD-1 inhibitors in comparison to wildtype patients regardless of PD-L1 level.[19] As with other analyses of patients with EGFR ex20ins NSCLC, the findings presented here were limited by the small number of patients in both the ICI and ICI-chemotherapy groups and even smaller numbers in later lines of therapy.

Conclusions

In conclusion, ICIs were prescribed for a substantive number of patients with EGFR ex20ins NSCLC in the real-world setting. Although ICIs are transformative in other subtypes of NSCLC, they may not be an effective therapy for patients with EGFR ex20ins NSCLC. These findings may inform future clinical trials of ICIs in EGFR ex20ins NSCLC and also stress the need for new treatment options for this underserved patient population.

Clinical Practice Points

- Patients with NSCLC harboring EGFR ex20ins are generally insensitive to EGFR TKIs. However, less is known about how this patient population responds to ICIs since many large immunotherapy-based trials have excluded patients with any type of EGFR mutations.
- In this retrospective study using real-world data, patients with EGFR ex20ins NSCLC were associated with a 58% increased risk of shorter time to next-line therapy after first ICI line as compared with patients with wildtype NSCLC.
- Although ICIs are transformative in other subtypes of NSCLC, they may not be an effective therapy for patients with EGFR ex20ins NSCLC.

Author Contributions

NG, AM, SIO, SMG, JT, SV, JMB, AL, PM, and *LB* contributed to conceptualization of the study. *AL* contributed to formal analysis. *NG* and *AL* contributed to data curation. *NG, AL*, and *PM* contributed to methodology. All authors contributed to writing and reviewing of the manuscript.

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Disclosure

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AM reports honoraria from Chugai Pharmaceuticals (teaching), Janssen (advisory board), Merck (advisory board), Novartis Oncology (teaching), Faron Pharmaceuticals (advisory board), and Bayer; and expenses from Loxo Oncology and Amgen. *SIO* was on the scientific advisory board (until April 2019) and has stock ownership of Turning Point Therapeutics, Inc., and Elevation Oncology; has received speaker honorarium from Merck, Roche/Genentech, AstraZeneca, Takeda/ARIAD, and Pfizer; and has received advisory fees from Roche/Genentech, AstraZeneca, Takeda/ARIAD, Pfizer, Foundation Medicine, Inc., Spectrum, X-Covery, Janssen/Johnson & Johnson, and Daiichi Sankyo. *SMG* reports consulting for Genentech/Roche, Janssen, Takeda, AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck, Pfizer, and Blueprint; and research funding from Merck and AstraZeneca. *JT* reports consulting or advisory role for BMS, Takeda, MSD, and Boehringer Ingelheim; speaker's bureau fees from MSD, Roche, Merck, AstraZeneca, Bayer, and Pfizer; and travel grant from BMS, MSD, and AstraZeneca. *SV* reports consulting or advisory role for AbbVie, Bristol Myers Squibb, Roche, Takeda, AstraZeneca, and MSD; speaker's bureau fees from Bristol-Myers Squibb, MSD, Roche and AstraZeneca; and travel expenses from Roche, OSE Pharma, Bristol-Myers Squibb, Merck, Merck Serono, Puma Biotechnology, and Janssen Cilag. *JMB* is a current employee of Janssen R&D; reports previous research/grant support from Merck, Clovis, Carevive Systems, Novartis, Bayer, Janssen, AstraZeneca, Takeda, and Carisma Therapeutics; and reports consultative services for Clovis, Bristol-Myers Squibb, AstraZeneca, Celgene, Boehringer Ingelheim, Janssen, Merck, Guardant Health, Genentech, Takeda, Ayala, Regeneron, Inivata, and Novartis. *AL* and *PM* are employees of Janssen Research & Development, LLC, and own stock and/or stock options. *LB* reports consultative services for Daiichi Sankyo, Boehringer Ingelheim, Janssen, Bristol-Myers Squibb, Merck, Novartis, and Regeneron; and research funding from BeyondSpring.

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