Response to Standard Therapies and Comprehensive Genomic Analysis for Patients with Lung Adenocarcinoma with *EGFR* Exon 20 Insertions

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ABSTRACT

Purpose: *EGFR* exon 20 insertions (ex20ins) are an uncommon genotype in non–small cell lung cancer (NSCLC) for which targeted therapies are under development. We sought to describe treatment outcomes and genomic and immunophenotypic characteristics of these tumors.

Experimental Design: We identified sequential patients with NSCLC with *EGFR* ex20ins and compared their clinical outcomes and pathologic features with other patients with NSCLC.

Results: Among 6,290 patients with NSCLC, 106 (2%) had *EGFR* ex20ins. Patients with *EGFR* ex20ins were more likely to be Black (14% vs. 6%; $P < 0.001$) or Asian (22% vs. 10%; $P < 0.001$) compared with all other patients with NSCLC. Median tumor mutational burden (TMB; 3.5 vs. 5.9; $P < 0.001$) and proportion of tumors with PD-L1 expression ≥1% (22% vs. 60%; $P < 0.001$) were lower in *EGFR* ex20ins compared with other NSCLCs (TMB, $n = 5{,}851$ and PD-L1 expression, $n = 282$) and *EGFR* del 19/L858R (median TMB, 3.5; $P = 0.001$ and 39% PD-L1 ≥ 1%; $P = 0.02$). Compared with a 2:1 cohort of patients with metastatic NSCLC without targetable alterations ($n = 192$), *EGFR* ex20ins patients had longer overall survival (median 20 vs. 12 months; HR, 0.56; $P = 0.007$) and longer time to treatment discontinuation (TTD) for platinum chemotherapy (median, 7 vs. 4 months; HR, 0.6; $P = 0.02$) and no improvement in TTD for immune checkpoint inhibitors (ICI; HR, 1.75; $P = 0.05$).

Conclusions: With better outcomes on platinum chemotherapy, patients with *EGFR* ex20ins NSCLC have improved prognosis, lower PD-L1 expression and TMB, and derive less benefit from ICIs compared with patients with NSCLC without targetable oncogenes. Improving molecularly targeted therapies could provide greater benefit for patients with *EGFR* ex20ins.

Introduction

The treatment of patients with metastatic non–small cell lung cancer (NSCLC) has evolved rapidly in recent years, as next-generation sequencing (NGS) has facilitated identification of new molecular targets and development of multiple generations of effective targeted therapies. The effectiveness of immune checkpoint inhibitors (ICIs) as monotherapy or combination therapy has further added to the repertoire of approved treatment options for NSCLC (1–5). Prior work has shown that molecular subtypes of NSCLC further influence response to standard treatments (6–8). In particular, patients with some oncogene-driven lung cancers have improved responses to chemotherapy compared with patients without oncogene-driven cancers (9, 10).

EGFR exon 20 insertions (ex20ins) are driver alterations that comprise approximately 4% to 10% of *EGFR*-mutant NSCLCs (11–13) and 2% of all NSCLCs (14–16). *EGFR* ex20ins preferentially maintain the regulatory C-helix element of EGFR in its active, outward conformation (17), while *EGFR* exon 19 deletions (del 19) and L858R alterations permit constitutive receptor activation by destabilizing the inactive form of EGFR and inducing greater affinity for ATP than wild-type EGFR (18, 19). Because of these conformational and mechanistic differences between classical sensitizing *EGFR* mutations and ex20ins, NSCLCs with *EGFR* ex20ins are generally insensitive to currently approved EGFR tyrosine kinase inhibitors (TKI) at standard doses (20–22), although limited responses to standard dosing osimertinib have also been reported (23, 24). A notable exception is *EGFR* A763_Y764insFQEA, an alteration found in the C-helix predicted to activate EGFR in a manner closely resembling classic sensitizing alterations, which has demonstrated sensitivity to multiple EGFR TKIs in both *in vitro* models and a limited number of patients (25–27).

Although there are no currently approved targeted therapies for *EGFR* ex20ins, it is an active area for drug development, with multiple promising molecularly targeted strategies in clinical trial testing. Several investigational agents, including mobocertinib (28) and amivantamab (29), have shown encouraging activity against *EGFR* ex20ins in early clinical trials. Osimertinib 160 mg, twice the standard dose, has shown activity in patients with *EGFR* ex20ins from preliminary trial results (30). The role and effectiveness of standard therapy in *EGFR* exon20ins remain unclear. A better understanding of the effectiveness of standard therapies in *EGFR* ex20ins is needed to assess whether investigational agents offer substantial benefit.

We sought to describe the clinical outcomes and response to standard therapies, including ICI, platinum-based chemotherapy, and combination chemo-ICI. We identified all patients with NSCLC and

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

An uncommon non–small cell lung cancer (NSCLC) genotype, *EGFR* exon 20 insertions (ex20ins), is the subject of active drug development, although no targeted therapies have yet been approved. The response to standard therapies for these cancers has not been well-characterized and is needed to serve as a benchmark to assess the efficacy of investigational agents in single-arm trials. We sought to describe the response to standard treatments for these patients and provide a comprehensive analysis of the molecular features of *EGFR* ex20ins NSCLC. Although responses to platinum chemotherapy are encouraging compared with NSCLC without targetable alterations, responses to immune checkpoint inhibitors are shorter. We report that *EGFR* ex20ins tumors have low PD-L1 tumor expression, low tumor mutational burden, and infrequent coalterations. Our results highlight the need for targeted therapies in this patient population.

EGFR ex20ins detected by NGS using Memorial Sloan Kettering Cancer Center (MSK)-IMPACT (31) at our institution and retrospectively evaluated their clinical outcomes compared with a historical cohort of NSCLC without targetable alterations.

Materials and Methods

Patient identification

We identified all patients with NSCLC whose tumors underwent genomic profiling with MSK-IMPACT (31) prior to July 2020 using the MSK clinical sequencing cohort in cBioPortal (32, 33). Patients with *EGFR* ex20ins were identified from this cohort, with *EGFR* ex20ins status verified by a diagnostic molecular pathologist. A 2:1 control cohort was selected consecutively from the remaining cases after removing all cases with known driver alterations in *EGFR, ALK, RET*, and *BRAF V600E*. All patients with *EGFR* ex20ins and the 2:1 control cohort underwent medical record review to obtain treatment history, pathology, and basic demographic information. Basic patient (age at which sequencing was performed, sex, and race) and tumor characteristics [histology, genomic results, and tumor mutational burden (TMB)] for all patients were collected from cBioPortal. As patient smoking histories were not collated for the entire cohort, but were of interest to us, we used a subgroup of patients with NSCLC included in the MSK-IMPACT clinical sequencing cohort where smoking histories were available from a previously published study (6), after removing patients with *EGFR* exon20ins. The study was conducted in accordance with recognized ethical guidelines and was approved by the MSK Institutional Review Board/Privacy Board (New York, NY).

Somatic alterations were determined using MSK-IMPACT, as has been described previously (31). Somatic alterations, including copy-number alterations (CNAs), were assessed for enrichment in *EGFR* ex20ins cases compared with unselected NSCLC cohort and a separate cohort of *EGFR* L858R/del 19 cases using Fisher exact test. To reduce false discovery in multiple testing, an FDR q value < 0.05 was applied using Benjamini–Hochberg procedure. TMB was calculated across each version of the MSK-IMPACT panel (341, 410, or 468 genes) and is defined as the total number of mutations divided by the coding region analyzed. TMB is reported as mutations/Mb. Only one sample was used per patient. If patients had multiple samples available, the sample with the highest tumor purity was selected for TMB analysis. PD-L1 expression was performed as part of routine clinical care and was scored as the percentage of tumor cells with membranous staining.

Statistical analysis

Patient and tumor characteristics were compared using Wilcoxon rank-sum test, χ^2 test of independence, or Fisher exact tests. Overall survival was defined from the date of first-line metastatic treatment to the date of death or last follow-up, with a data lock on July 15, 2020. Time to treatment discontinuation (TTD) was defined from the first date of treatment to the decision date of treatment termination or last follow-up; patients were censored if they remained on treatment by July 15, 2020. Overall survival and TTD probabilities were computed using Kaplan–Meier estimates, with left truncation to account for the time of MSK-IMPACT. For the delayed entry Kaplan–Meier analyses, patients may enter the risk set post-baseline if their IMPACT data were recorded after the start of treatment. Patients were also excluded if full treatment details, such as date of first-line therapy or reason for therapy discontinuation, were unknown. The comparative analysis for the time to event endpoints with respect to *EGFR* exon 20 mutation status was computed using the log-rank test with left truncation.

Results

Patient and tumor characteristics

From July 2014 to July 2020, 106 patients with *EGFR* ex20ins were identified of 6,290 (2%) patients with NSCLC with MSK-IMPACT results and 1,507 (7%) with any *EGFR* mutation. Of these, 59 (56%) were diagnosed in the metastatic setting and 47 (44%) at an earlier stage, with 17 disease recurrences during the study period (Supplementary Fig. S1). Compared with the remaining 6,184 patients with NSCLC without *EGFR* ex20ins, *EGFR* ex20ins patients were younger (median age, 66 vs. 69; $P < 0.001$), were more frequently women (69% vs. 58%; $P = 0.03$), and Black (14% vs. 6%; $P = 0.001$) or Asian (22% vs. 10%; $P < 0.001$; **Table 1**). As has been described previously (11, 13), the majority of *EGFR* ex20ins patients had adenocarcinoma histology (96% vs. 76%; $P < 0.001$) and were never or light former smokers (88% vs. 52%; $P < 0.001$) compared with a subgroup of patients with smoking history available ($n = 985$).

We identified 15 distinct ex20ins alterations. The most commonly observed were S768_D770 duplication ($n = 22$, 21%), A767_V769 duplication ($n = 20$, 19%), and N771_H773 duplication ($n = 13$, 12%; **Fig. 1**).

Clinical outcomes and response to therapy

We next evaluated survival from initiation of first-line metastatic treatment. With a median follow-up of 1.3 years (range, 0.2–17 years), 62 patients with *EGFR* ex20ins and 192 patients without driver alterations were included. Median survival for patients with *EGFR* ex20ins was 20 months [95% confidence interval (CI) 17 months to not reached], compared with 12 months for patients without targetable alterations (95% CI, 10–15 months), with HR 0.56 (95% CI, 0.37–0.86; $P = 0.007$; **Fig. 2A**).

Given well-established data that patients with *EGFR* ex20ins do not benefit from currently approved EGFR TKIs at standard doses, we focused on TTD for standard therapies for metastatic NSCLC: platinum-based doublet therapy +/− bevacizumab, ICI, and chemo-ICI. In this analysis, 31 patients with *EGFR* ex20ins and 94 patients with NSCLC without targetable alterations who received platinum chemotherapy in the metastatic setting (Supplementary Table S1) were included. The most common reason for treatment discontinuation was progressive disease

Table 1. Patient characteristics: basic demographic information was compared between the 106 patients with *EGFR* ex20ins and all other patients with NSCLC who underwent genomic profiling with MSK-IMPACT.

	***EGFR* ex20ins *n* = 106 *n* (%)**	**NSCLC without *EGFR* ex20ins *n* = 6,184 *n* (%)**	
Age, median (range)	66 (30–90)	69 (13–90)	$P < 0.001$
Sex			$P = 0.03$
Male	33 (31)	2,586 (42)	
Female	73 (69)	3,585 (58)	
Not stated	0 (0)	13 (<1)	
Race			
White	61 (62)	4,875 (84)	$P < 0.001$
Asian	22 (22)	583 (10)	$P < 0.001$
Black	14 (14)	318 (6)	$P = 0.001$
Native American	0 (0)	9 (<1)	
Hawaiian/Pacific Islander	1 (1)	5 (<1)	
Not known	8 (8)	394 (6)	
Histology			$P < 0.001$
Adenocarcinoma	102 (96)	4,735 (76)	
Squamous	0 (0)	655 (11)	
Large cell/ neuroendocrine	0	142 (2)	
Poorly differentiated	4 (4)	387 (6)	
Other	0 (0)	277 (4)	
Smoking history		*n* = 985	$P < 0.001$
Never smoker	63 (59)	314 (32)	
≤15 py	31 (29)	192 (20)	
>15 py	12 (11)	468 (48)	
Not known	0	11 (1)	

Note: "Other" histologies include carcinoid, sarcomatoid, adenosquamous, lymphoepithelial, and basaloid, among other rare histologies.
Abbreviation: py, pack-years of smoking history.

(PD), which occurred in 65% of patients with EGFR ex20ins and 70% of those patients without targetable oncogenic drivers. Patients with *EGFR* ex20ins had longer TTD on platinum-based chemotherapy compared with patients without targetable alterations, with median time of 7 versus 4 months (HR, 0.60; 95% CI, 0.39–0.93; $P = 0.02$; **Fig. 2B**).

The next most common standard therapy received was ICI treatment with anti–PD-1 or anti–PD-L1 antibodies, with 15 *EGFR* ex20ins and 99 patients in the control group included. Among *EGFR* ex20ins, six (40%), five (33%), and four (27%) patients received ICI as the first, second, or third or greater line of treatment, compared with 72% of patients in the control group receiving ICI as second-line treatment. All *EGFR* ex20ins patients discontinued ICI for PD, compared with 77 (78%) patients in the control group, with the remaining 10 patients in the control group discontinuing ICI for toxicity. Duration of treatment with ICI was not different for patients with and without *EGFR* ex20ins (median TTD, 2.8 vs. 2.8 months; HR, 1.75; 95% CI, 1–3.1; $P = 0.05$; **Fig. 2C**). We also assessed outcomes for the small subset of patients who received chemo-ICI, including 12 patients with *EGFR* ex20ins and 36 patients in the control group. The most common treatment given was carboplatin, pemetrexed, and pembrolizumab. The median time on chemo-ICI was similar for patients with *EGFR* ex20ins and patients in the control group (median, 7 vs. 5 months; HR, 1.1; 95% CI, 0.52–2.41; $P = 0.8$; **Fig. 2D**).

Genomic and immunophenotypic characteristics

To determine whether known prognostic and predictive factors were different in patients with *EGFR* ex20ins, we compared genomic and immunophenotypic characteristics of *EGFR* ex20ins tumors with all NSCLCs without *EGFR* ex20ins and tumors with classical *EGFR* alterations (del 19 and L858R). Of the 6,290 unique patients with NSCLC with MSK-IMPACT available at the time of analysis, 1,088 patients had *EGFR* del 19 or L858R. The TMB in tumors with *EGFR* ex20ins [median TMB, 3.4; interquartile range (IQR), 1.8–4.6; $n = 106$] was lower than that observed in *EGFR* del 19/L858R (median, 3.5; IQR, 2.6–5.6; $P = 0.001$; $n = 1058$) and NSCLC without *EGFR* ex20ins (median, 5.9; IQR, 3–10; $P < 0.001$; $n = 5{,}851$; **Fig. 3A**). Among available tumor samples, a higher proportion of tumors with *EGFR* del 19/L858R had PD-L1% expression ≥1% compared with *EGFR* ex20ins tumors (39% vs. 22%; $P = 0.02$, Fisher exact test). A higher proportion of tumors without *EGFR* ex20ins also had PD-L1 expression ≥1% compared with *EGFR* ex20ins tumors (60% vs. 22%; $P < 0.001$, Fisher exact test; **Fig. 3B**).

We next evaluated the frequency of cooccurring genomic alterations. Comutations that were observed in the *EGFR* ex20ins cohort at a frequency ≥5% were in *TP53* (48%), *CTNNB1* (6%), and *U2AF1* (6%). CNAs observed at ≥5% frequency were *EGFR* amplifications (17%), deletions in *CDKN2A* (17%) and *CDKN2B* (16%), and amplifications in *NKX2–1* (12%), *FOXA1* (8%), and *TERT* (8%; **Fig. 4A**). We identified that alterations in *KRAS* (27%, any alteration), *STK11* (13%), *KEAP1* (13%), *NF1* (7%), *PTPRT* (7%), *RBM10* (10%), *KMT2D* (8%), *SETD2* (5%), and *PTPRD* (9%) occurred more frequently in tumors without *EGFR* ex20ins, while mutations in *EGFR* (100% vs. 24%) and *CTNNB1* (9% vs. 3%) were more common in tumors with *EGFR* ex20ins ($P < 0.001$; $q < 0.05$ by Benjamini–Hochberg; **Fig. 4B**). *EGFR* (15% vs. 6%) and *RBM10* (4% vs. 0.3%) amplifications were also enriched in tumors with *EGFR* ex20ins ($P < 0.001$; $q < 0.03$; **Fig. 4C**). We next compared the genomic landscape of *EGFR* ex20ins with classical *EGFR* del 19 and L858R cases, but there were no somatic alterations associated with either cohort that met our statistical thresholds. There were no CNAs enriched in *EGFR* ex20ins cases compared with *EGFR* del 19/L858R cases.

Discussion

In this analysis, we have described the clinical outcomes of patients with *EGFR* ex20ins NSCLC, an uncommon driver alteration in NSCLC, as well as the molecular features of these tumors. We found that *EGFR* ex20ins occurred in 2% of all patients with NSCLC and in 7% of patients with *EGFR*-mutant lung cancers. Overall, we found that *EGFR* ex20ins were more prevalent in Black patients, Asian patients, and never smokers and that patients with *EGFR* ex20ins have a somewhat greater benefit with platinum-based chemotherapy than patients with NSCLC without a targetable alteration.

Prior reports on clinical outcomes of *EGFR* ex20ins patients have largely focused on the lack of response to EGFR TKIs and have provided limited data on response to cytotoxic and immune-based NSCLC therapies. Our analysis may serve as a benchmark to assess the efficacy of multiple investigational agents targeting *EGFR* ex20ins in single-arm clinical trials. In other molecularly defined NSCLC populations, targeted therapies for EGFR and ALK alterations have shown clear survival and response benefits over chemotherapy, as would be expected of oncogene-addicted cancers dependent on driver alterations (34–41). In our North American cohort, we found that patients with *EGFR* ex20ins have encouraging responses to platinum chemotherapy, with median TTD of 7 months that was superior to

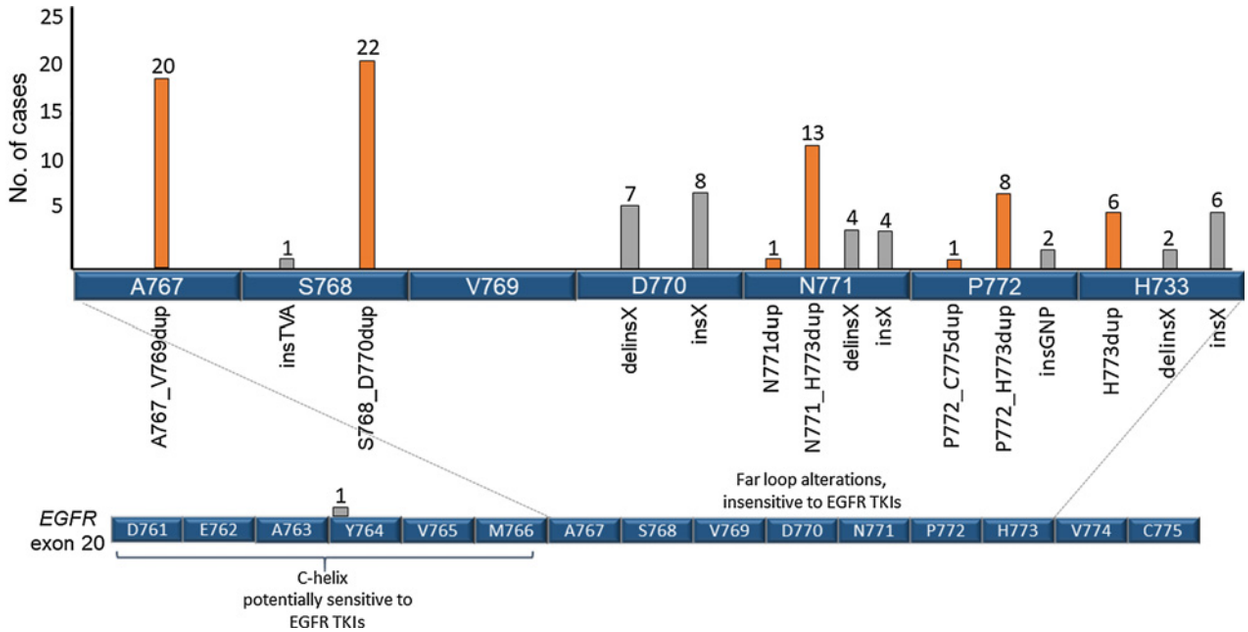

Figure 1.

Ex20ins. Fifteen distinct *EGFR* ex20ins were identified. The locations and number of each insertion are identified, along with amino acids 761D–766M, which comprise the regulatory C-helix. Only one insertion (A763_Y764insFQEA) was found in the C-helix; this alteration is predicted to be sensitizing to EGFR TKIs. Amino acids 767A–775C compose the loop following the C-helix (far loop alterations) where the majority of *EGFR* ex20ins events occur. Duplication events are labeled in orange and other insertion events are in gray.

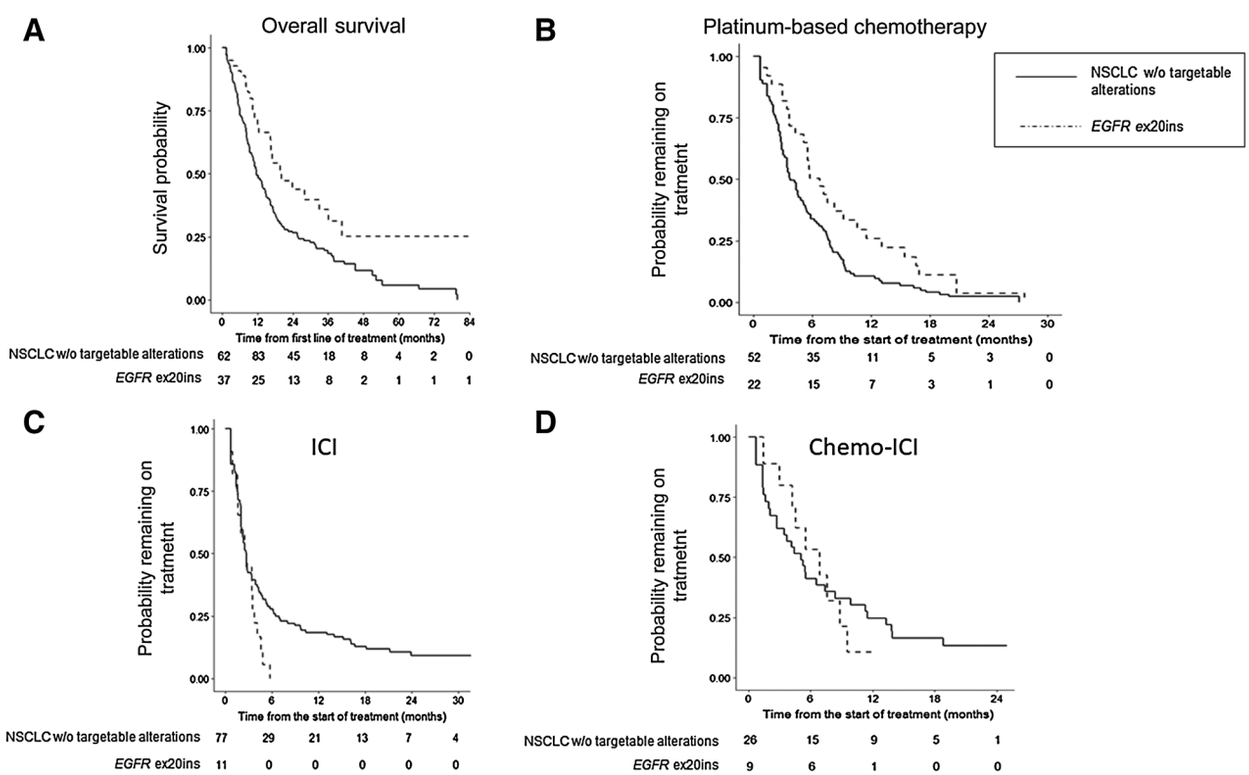

Figure 2.

Clinical outcomes. **A,** Overall survival for *EGFR* ex20ins cohort was compared with patients with NSCLC without targetable driver alterations. **B,** TTD on platinum chemotherapy. **C,** TTD for ICI. **D,** TTD for chemo-ICI. To account for left truncation, any cases where MSK-IMPACT resulted after end of treatment, date of death, or last clinic follow-up were excluded. For the delayed entry Kaplan–Meier analyses, patients may enter the risk set postbaseline if their IMPACT data were recorded after the start of treatment.

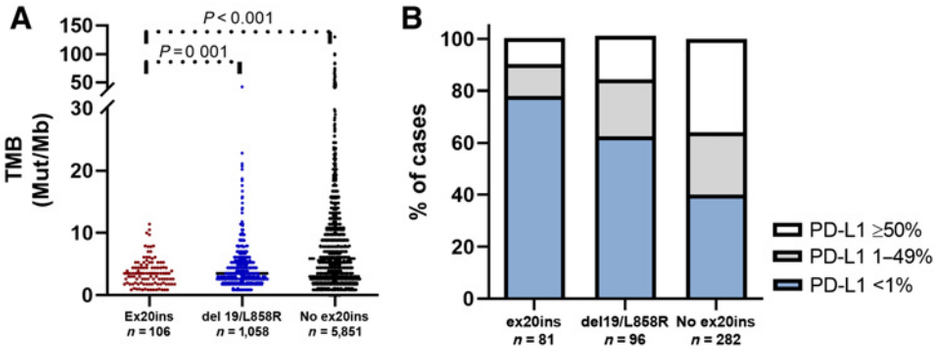

Figure 3.
Immunophenotype of ex20ins cases. **A,** Median TMB from available cases was significantly lower in *EGFR* ex20ins cases compared with both *EGFR* del 19/L858R tumors and NSCLC tumors without *EGFR* ex20ins. **B,** Tumor PD-L1 expression was quantified as low (<1%), intermediate (1%–49%), and high (≥50%) for available cases and tabulated across ex20ins, *EGFR* del19/L858R cases, and NSCLC without *EGFR* ex20ins tumors.

responses observed in an NSCLC cohort without driver alterations. These results are in concordance with these previously published studies. A study of Chinese patients with *EGFR* ex20ins reported a progression-free survival (PFS) of 6 months on first-line platinum-based chemotherapy (42). A study of 22 Korean patients reported a 50% objective response rate (ORR) with platinum chemotherapy (43). One possible explanation for this finding is that oncogene-addicted NSCLC is more sensitive to pemetrexed, with which all patients with

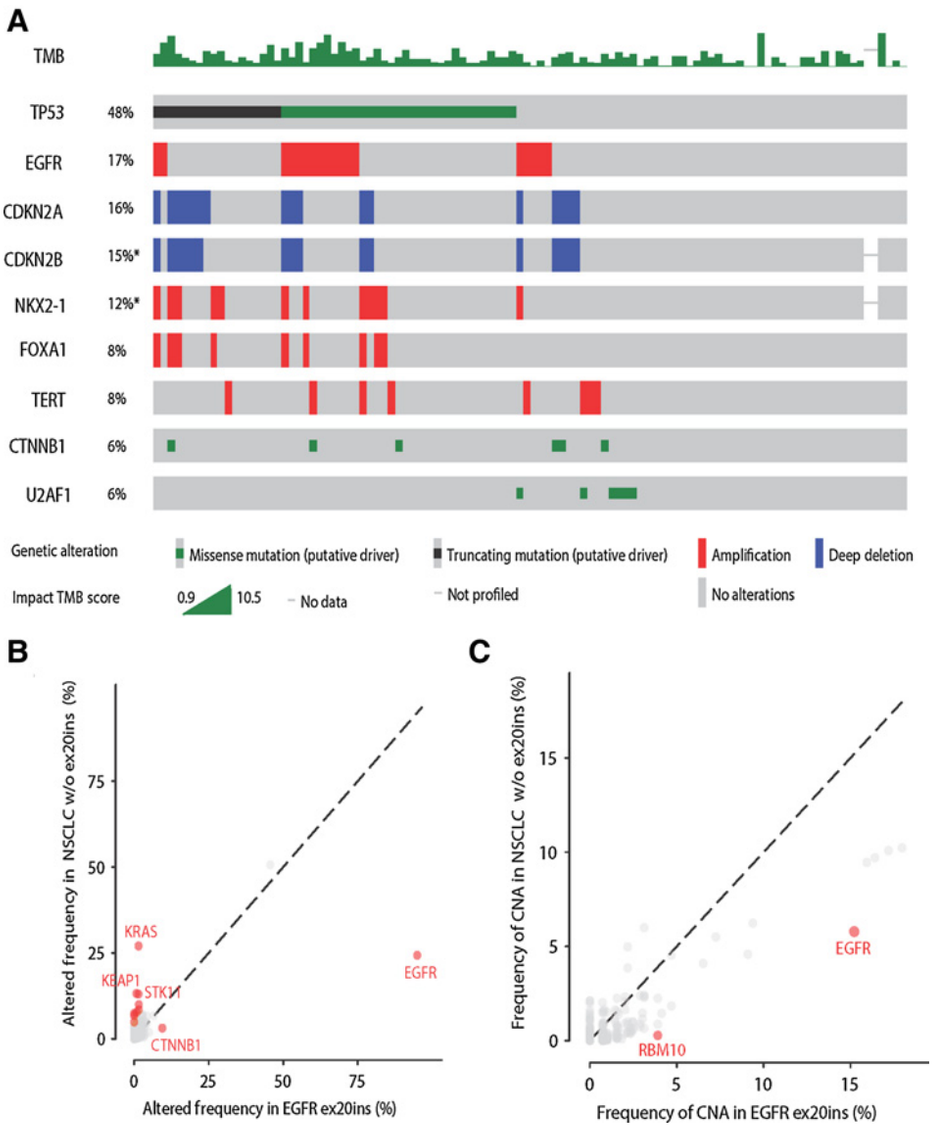

Figure 4.
Genomic landscape of *EGFR* ex20ins. **A,** Oncoprint of the mutations and copy-number alterations (CNAs) found at ≥5% frequency among ex20ins cases, with TMB quantified at top of graph. **B,** Frequency of altered genes in *EGFR* ex20ins cohort compared with NSCLC without *EGFR* ex20ins. Genes highlighted in red designate $q < 0.05$. **C,** Frequency of CNA in the *EGFR* ex20ins cohort compared with other NSCLC cases.

EGFR ex20ins were treated, than other NSCLCs. This has been demonstrated with other oncogene-driven NSCLCs, including patients with *ALK* (9, 44), *ROS1* (45), and *RET* (10) alterations. Given the low number of patients in our cohorts treated with chemo-ICI, future studies are required to evaluate whether patients with *EGFR* ex20ins derive greater clinical benefit from chemo-ICI compared with platinum chemotherapy. This remains an important question to answer as it will enable clinicians to appropriately sequence therapies, but of note, combination platinum chemotherapy and pembrolizumab is not FDA approved for patients with *EGFR* mutations (46).

The suboptimal response to ICI observed among patients with *EGFR* ex20ins aligns with previous observations that ICIs have poor activity in patients with NSCLC with driver alterations. A series of *EGFR*-mutant lung cancers previously reported poor responses to ICIs (47). In the IMMUNOTARGET registry, patients with the common *EGFR* exon del 19 or L858R mutations, or fusions in *RET, ROS1*, or *ALK* had ORRs to ICI <20% and PFS less than 3.5 months (48). This may be explained partially by low tumor PD-L1 expression and low TMB, which have been consistently reported in NSCLC tumors with driver alterations (49). However, recent work suggests that PD-L1 expression does not predict responsiveness to immune checkpoint blockade in patients with *EGFR* exon del 19 or L858R cancers (50) and may be of limited utility in predicting responsiveness to ICIs in *EGFR*-mutant lung cancer. A further consideration for potentially avoiding ICIs in patients with *EGFR* ex20ins is the risk for severe immune-related adverse events if osimertinib is given following ICIs, as has been demonstrated in patients with sensitizing *EGFR* alterations (51). Overall, our results suggest that ICIs may not be a fruitful later-line therapy for patients with *EGFR* ex20ins.

Given the rarity of *EGFR* ex20ins, the overall number of patients receiving each line of therapy is a limitation of this single-institution retrospective study. In this retrospective analysis, we used TTD rather than RECIST-based response rate or PFS to assess clinical efficacy, although TTD may approximate PFS (52). Our study population was also heterogeneous and received each category of treatment at varying timepoints of metastatic disease, which may confound the responses reported. Finally, a source of potential bias is that all patients included in our study underwent genomic profiling with MSK-IMPACT, which resulted in fewer patients with squamous cell carcinoma included in the comparator cohort (estimated real-world prevalence 30%, compared with 11% prevalence in our cohort). Despite these limitations, this study remains among the largest cohorts of patients with *EGFR* ex20ins reported. The distribution of unique *EGFR* ex20ins in our cohort is similar to previous reports, with the majority of insertions occurring in the far loop region following the C-helix (26, 53, 54). However, our cohort included only 1 patient with A763_Y764insFQEA, an alteration sensitizing to EGFR TKIs, while other studies have cited frequencies of 5% to 10%.

In summary, we describe here comprehensive genomic, immunophenotypic, and clinical outcomes of patients with *EGFR* ex20ins. We anticipate that patients with *EGFR* ex20ins will be increasingly recognized and understanding the response to standard therapies will help clinicians determine what treatments to offer to patients unable to enroll in clinical trials or who have exhausted trial options. Our analysis demonstrates that with low TMB and low PD-L1, *EGFR* ex20ins tumors are similar to *EGFR* del 19/L858R in genomic landscape and have relatively few genomic or immunophenotypic vulnerabilities to exploit with standard therapy options after progression on platinum-based chemotherapy. Given the promising activity of several investigational targeted therapies for *EGFR* ex20ins, these remain the preferred option for patients with *EGFR* ex20ins over later-line ICI or non-platinum chemotherapy.

Authors' Disclosures

C.M. Rudin reports personal fees from Amgen, AstraZeneca, Celgene, Epizyme, Genentech/Roche, Ipsen, Jansen, Jazz, Lilly, Pfizer, PharmaMar, Syros, Vivotek, Bridge Medicines, Earli, and Harpoon outside the submitted work. M.G. Kris reports personal fees from AstraZeneca, Genentech/Roche, Daiichi Sankyo, Sanofi/Genzyme, Pfizer, Novartis, and Regeneron outside the submitted work. M.E. Arcila reports personal fees from Invivoscribe, Biocartis, and AstraZeneca outside the submitted work. H.A. Yu reports other from Cullinan Oncology and AstraZeneca during the conduct of the study, other from Daiichi Sankyo, Novartis, Pfizer, and Lilly, personal fees from Blueprint Medicine, and personal fees and other from Janssen Oncology outside the submitted work. M. Ladanyi reports personal fees from Janssen and Takeda outside the submitted work. G.J. Riely reports grants from Ramapo Fund and John and Georgia DallePezze during the conduct of the study and from Mirati, Pfizer, Takeda, Roche, Novartis, and Merck outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

N.J. Choudhury: Conceptualization, data curation, formal analysis, writing–original draft, writing–review and editing. **A.J. Schoenfeld:** Conceptualization, data curation, writing–review and editing. **J. Flynn:** Formal analysis, writing–review and editing. **C.J. Falcon:** Data curation, writing–review and editing. **H. Rizvi:** Data curation, writing–review and editing. **C.M. Rudin:** Resources, writing–review and editing. **M.G. Kris:** Resources, writing–review and editing. **M.E. Arcila:** Resources, writing–review and editing. **G. Heller:** Formal analysis, methodology, writing–review and editing. **H.A. Yu:** Resources, writing–review and editing. **M. Ladanyi:** Resources, writing–review and editing. **G.J. Riely:** Conceptualization, resources, formal analysis, supervision, funding acquisition, methodology, writing–original draft, writing–review and editing.

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