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 ex20ins remains 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...
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 encouraged 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.

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. 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.

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.

Standard Therapies in NSCLC with EGFR Exon 20 Insertions

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, \( \chi^2 \) 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.
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.

<table>
<thead>
<tr>
<th>EGFR ex20ins</th>
<th>NSCLC without EGFR ex20ins</th>
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<tr>
<td><strong>n = 106</strong></td>
<td><strong>n = 6,184</strong></td>
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<tr>
<td>Age, median (range)</td>
<td>66 (30–90)</td>
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<td>Hawaiian/Pacific Islander</td>
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Note: “Other” histologies include carcinoid, sarcomatoid, adenosquamous, lymphoepithelial, and basaloid, among other rare histologies. Abbreviation: py, pack-years of smoking history.

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 NSCLC 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 NKF2–1 (12%), FOXA1 (8%), and TERT (8%; Fig. 4A). We identified that alterations in KRAS (27%, any alteration), STK11 (13%), KEAPI (13%), NFI (7%), PTPT (7%), RB10 (10%), KMT2D (8%), SETD2 (5%), and PTPT (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 Benjamin–Hochberg; Fig. 4B). EGFR (15% vs. 6%) and RB10 (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 comprise 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.
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...
EGFR ex20ins were treated, 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 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 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_Y764insF-QEA, 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, Epiyyme, Genentech/Roche, Ipsen, Jansen, Jazz, Lilly, Pfizer, PharmaMar, Syros, Vivotek, Bridge Medicines, Earl, 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 Invivovaccine, Bocartis, 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. Riel reports grants from Ramapo Fund and John and Georgia DallePeze 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. Rivi: 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. Riel: Conceptualization, resources, formal analysis, supervision, funding acquisition, methodology, writing—original draft, writing—review and editing.

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