ORIGINAL ARTICLE

Natural History and Real-World Treatment Outcomes for Patients With NSCLC Having *EGFR* Exon 20 Insertion Mutation: An International Association for the Study of Lung Cancer–American Society of Clinical Oncology CancerLinQ Study

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ABSTRACT

Introduction: EGFR exon 20 insertion (ex20ins) mutations account for approximately 10% of EGFR mutations in lung adenocarcinoma. Patients with ex20ins mutation do not respond to standard EGFR tyrosine kinase inhibitor therapy. In this work, we analyzed the characteristics, treatment patterns, and outcomes in this subgroup of patients with NSCLC.

Methods: The American Society of Clinical Oncology CancerLinQ Discovery data set was queried to identify patients with initial diagnosis of NSCLC between the years 1995 and 2018 and with EGFR ex20ins mutations. Data were extracted on patient demographics, tumor characteristics, treatments, and outcomes, and compared using chi-square and analysis of variance. Kaplan-Meier curves were generated to compare overall survival with log-rank tests. All analyses were performed using Python 3.6 (Python Software Foundation).

Results: A total of 357 patients were eligible. Patient characteristics include a median age of 68 years comprising female sex of 54%, White race of 63%, and Black race of 9%. Approximately 62% of total patients had stage 4 disease, and 30% of all patients had brain metastasis. There were 54% of patients who were treated with chemotherapy and 15% with immune checkpoint inhibitors (ICIs). In patients with brain metastasis, 16% were treated with ICI, 18% with targeted therapy, and 59% with chemotherapy. The median survival of the entire group was 23.8 months. Among patients with stage 4 disease (n = 222): 51% were women, 64% were white, 37% had brain metastasis, 18% were treated with ICI, 14% had targeted therapy, and 60% were treated with chemotherapy. Stage 4 patients treated with targeted therapy had better survival compared with those who did not receive targeted therapy (20.6 versus 16.1 mo, $p = 0.02$). Univariate and multivariate analyses suggested favorable outcomes for patients treated with immunotherapy.

Conclusions: EGFR ex20ins mutation represents a unique subset of NSCLC; it is associated with a higher propensity

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for brain metastases and a relatively modest overall survival. Novel treatment approaches are urgently needed to improve patient outcomes.

Keywords: EGFR Exon20; NSCLC; CancerLinQ; Real-world data IASLC

Introduction

Mortality related to lung cancer has started to decline in the United States.[1] This has been attributed to several factors including improvements in therapeutic options. Personalized therapy approaches on the basis of driver mutation status and programmed death-ligand 1 expression is routinely used for the treatment of patients with stage IV NSCLC, particularly for patients with adenocarcinoma histologic diagnosis. In lung adenocarcinoma, at least nine different targetable molecular abnormalities have therapeutic options approved by the U.S. Food and Drug Administration that provide robust efficacy results. Mutations in EGFR account for approximately 15% of lung adenocarcinoma in the western patient population. The most typically occurring EGFR mutations are exon 19 deletions and exon 21 L858R substitutions and account for approximately 85% of the EGFR mutations in NSCLC.[2] It is well established from clinical studies that treatment of patients with NSCLC harboring these common mutations with EGFR tyrosine kinase inhibitors (TKIs) is associated with improved outcomes.[2–4] The approved TKIs, such as erlotinib, gefitinib, afatinib, dacomitinib, and osimertinib have been found to be highly effective for the treatment of patients with NSCLC with EGFR mutations.[4–7]

Exon 20 insertion (ex20ins) is a rare type of mutation in the *EGFR* gene located primarily within codon 762 to codon 774 and accounts for approximately 4% to 10% of all EGFR mutations in patients with NSCLC.[8–10] However, in contrast to the common EGFR mutations, patients with NSCLC with ex20ins mutations do not respond well to TKIs.[8,10–13] The response rate with first and second-generation EGFR TKI in this population is less than 10% with a median survival of only approximately 9 months.[14,15] Osimertinib is currently under investigation in an ongoing clinical trial with initial results revealing a response rate of approximately 25%.[16] In 2021, the U.S. Food and Drug Administration approved two new therapeutic agents for this patient population; the approval for both amivantamab and mobocertinib is for patients who develop disease progression after previous platinum-based chemotherapy. It is hoped that the entry of these new agents into the therapeutic arena will accelerate the pace of progress for this patient population.

In this work, the International Association for the Study of Lung Cancer and American Society of Clinical Oncology (ASCO) CancerLinQ collaborated to analyze the characteristics, treatment patterns, and outcomes of patients with NSCLC harboring EGFR ex20ins mutations using the ASCO CancerLinQ Discovery (CLQD) data set to serve as benchmarks before the approval of targeted therapies and to serve as comparators to measure future progress. We also studied the potential impact of immune checkpoint inhibitor (ICI) therapy for this patient subset.

Materials and Methods

Data Source

CancerLinQ, developed in 2014 as a subsidiary of ASCO, is a nonprofit, big-data, and health technology platform in cancer. It has followed an electronic health record–agnostic approach to provide a harmonized data repository with structured and unstructured data captured from participating oncology organizations and practices. By March 2020, it included data from 63 organizations across the United States that use nine different electronic health record.[17] The CLQD was created as part of an initiative to make deidentified, real-world data available for research.[18] Because the CLQD database is a secondary source of data, which collected and included only deidentified data with no patient-identifiable information, institutional review board approval and patient consent were not required for this retrospective analysis.

Study Population

The CLQD data set was queried to identify patients with initial diagnosis of NSCLC between the years 1995 and 2018. Deidentified patient information was abstracted from the data files for this work. All patients that harbored EGFR ex20ins mutation were included in this analysis.

Study Variables

Patient information related to demographic data including age, sex, race, year of diagnosis, and geographic location was extracted. Patients of all stages were included in this work and grouped into three cohorts on the basis of American Joint Committee on Cancer staging system (stage I versus stage II/III versus stage IV). The treatment variables included in this analysis included targeted therapy, chemotherapy, and immunotherapy.

Study Outcomes

Overall survival (OS) was investigated as the primary outcome in this analysis. Those alive at the last follow-up were censored. Stage IV patients were analyzed as a distinct subgroup.

Statistical Analysis

Statistical analysis was conducted using Python version 3.6 (Python Software Foundation). Descriptive statistics for the overall population and the stage IV group were reported. Differences between groups were assessed using the chi-square test for categorical covariates and analysis of variance for numerical covariates. The univariate association of each covariate with OS was assessed using Cox proportional hazards models and log-rank tests followed by multivariate analyses of the covariates in the entire patient group and the stage 4 group. Kaplan-Meier plots were produced to compare the survival curves by treatment subgroups along with log-rank p value. Statistical significance was assessed at the 0.05 level, and all tests were two-sided unless otherwise noted.

Results

Patient Characteristics

A total of 357 patients with EGFR ex20ins were identified, with most of the patients diagnosed in 2005 and later. Patient characteristics are outlined in Table 1. The median age of the group is 68 years with 54% being women. The White race comprised 63% of the group. Approximately 62% of total patients had stage 4 disease, and 30% of all patients had brain metastasis.

Table 1. Patient Demographics

Variable Name	Level	n (%), N = 357
Sex	Female	191 (53.5)
	Male	166 (46.5)
Race	White	225 (63.0)
	Unknown	52 (14.6)
	Other Race	36 (10.1)
	Black or African American	32 (9.0)
	Asian	11 (3.1)
	American Indian or Alaska Native	1 (0.3)
Ethnicity	Not Hispanic or Latino	287 (80.4)
	Unknown	63 (17.6)
	Hispanic or Latino	7 (2.0)
U.S. Region	South Region	136 (38.1)
	Midwest Region	104 (29.1)
	Northeast Region	72 (20.2)
	Unknown	45 (12.6)
Death	Yes	243 (68.1)
	No	114 (31.9)
Immune checkpoint inhibitor	Yes	52 (14.6)
	No	305 (85.4)
Chemotherapy	Yes	192 (53.8)
	No	165 (46.2)
Brain metastasis	Yes	107 (30.0)
	No	250 (70.0)
Targeted therapy	Yes	43 (12.0)
	No	314 (88.0)
Surgery	Yes	85 (23.8)
	No	272 (76.2)
Stage group	4	222 (62.2)
	3	72 (20.2)
	1	24 (6.7)
	2	21 (5.9)
	Unknown	18 (5.0)
Age	Mean	67.8
	Median	68
	Minimum	27
	Maximum	93
	Std	10.9
	Missing	0
Follow-up time (mo)	Mean	25.4
	Median	18.1
	Minimum	0.4
	Maximum	184.8
	Std	27.4
	Missing	0.0

Std, standard deviation.

Treatment Patterns

Approximately 54% of the patients were treated with chemotherapy, 15% with ICIs (pembrolizumab, nivolumab, atezolizumab, durvalumab), and 12% with targeted therapy (erlotinib, gefitinib, afatinib, osimertinib). Approximately 24% of the patients underwent surgery. Of the patients who received checkpoint inhibitors, nearly 90% also received chemotherapy. Targeted therapy was administered to about 6% of the patients who received checkpoint inhibitors. In the patient group with brain metastases, 59% received chemotherapy; 16% were treated with checkpoint inhibitors, and 18% with targeted therapy.

Overall Survival

The median survival for the entire group is 23.8 months. The univariate analysis for OS revealed patients treated with ICI, chemotherapy, and targeted therapy were associated with a numerically lower risk of death compared with those not treated (Table 2) and surgery being associated with significantly improved survival (hazard ratio [HR] = 0.54, 95% confidence interval [CI]: 0.42–0.69, $p < 0.001$). These results are further confirmed with multivariable analysis of OS. On multivariable analysis of OS (Table 3), the female sex was associated with a higher risk of death compared with

Table 2. Univariable Analysis for Overall Survival

Covariate	Level	n	HR (95% CI)	HR *p* Value
ICI	Yes	52	0.76 (0.57-1.02)	0.067
	No	305	REF	
Chemotherapy	Yes	192	0.46 (0.17-1.20)	0.114
	No	165	REF	
Brain metastasis	Yes	107	1.19 (0.95-1.50)	0.133
	No	250	REF	
Targeted therapy	Yes	43	0.75 (0.55-1.04)	0.082
	No	314	REF	
Surgery	Yes	85	0.54 (0.42-0.69)	**<0.001**
	No	272	REF	
Sex	Female	191	1.48 (1.20-1.83)	**<0.001**
	Male	166	REF	
Race	American Indian or Alaska Native	1	6.10 (0.84-44.2)	0.073
	Asian	11	0.86 (0.47-1.58)	0.625
	Black or African American	32	0.85 (0.59-1.24)	0.406
	Other Race	36	1.04 (0.73-1.48)	0.828
	Unknown	52	0.84 (0.62-1.14)	0.269
	White	225	REF	
Ethnicity	Hispanic or Latino	7	0.69 (0.33-1.47)	0.342
	Unknown	63	0.88 (0.67-1.16)	0.376
	Not Hispanic or Latino	287	REF	
Region	Unknown	45	0.91 (0.65-1.27)	0.572
	Northeast Region	72	1.08 (0.81-1.44)	0.592
	Midwest Region	104	0.86 (0.67-1.11)	0.257
	South Region	136	REF	
Stage	3	72	0.68 (0.52-0.88)	**0.004**
	2	21	0.42 (0.27-0.67)	**<0.001**
	1	24	0.43 (0.28-0.66)	**<0.001**
	Unknown	18	0.63 (0.39-1.02)	0.061
	4	222	REF	

Bold *p*-value: statistically significant.
CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; REF, reference.

male sex (HR = 1.47, 95% CI: 1.18–1.84, $p < 0.001$). Black race was associated with a significantly lower risk of death compared with White race (0.62 , 95% CI: 0.42–0.91, $p < 0.016$). Patients treated with either ICI, chemotherapy, or targeted therapy exhibited favorable survival.

Analysis of Stage IV Patients

Among patients with stage 4 disease: 51% were women, 64% were white, and 37% had brain metastasis. Approximately 18% of stage 4 patients were treated with ICI, 14% received targeted therapy and 60% were treated with chemotherapy. For stage 4 patients, the median survival was 16.8 months. On Kaplan-Meier analysis, stage 4 patients who received ICIs had significantly better survival versus those who did not (median OS 29.1 versus 14.7 mo, $p = 0.01$) (Fig. 1). Stage 4 patients treated with ICI and chemotherapy had better survival compared with those treated with chemotherapy alone (median OS 29.1 versus 16.5 mo, $p = 0.05$) (Fig. 2). Stage 4 patients treated with targeted therapy had better survival compared with those who did not receive targeted therapy (median OS 20.6 versus 16.1 mo, $p = 0.02$) (Fig. 3).

On univariate analysis of survival for stage 4 patients, no statistically significant differences were seen on the basis of treatment received (Table 4). However, on multivariable analysis (Table 5), patients receiving ICI (HR = 0.65, 95% CI: 0.45–0.95, $p = 0.026$) and patients receiving targeted therapy (HR = 0.40, 95% CI: 0.24–0.65, $p < 0.001$) exhibited improved survival compared with those that did not receive these treatments.

Discussion

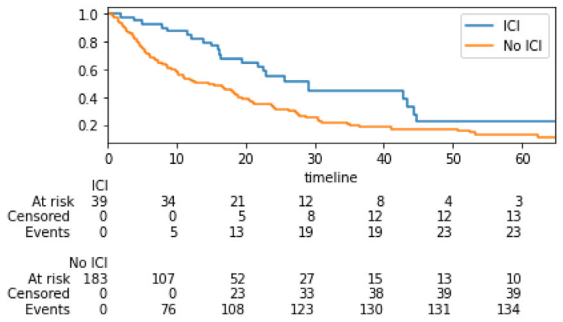
The discovery of EGFR mutation in lung adenocarcinoma and subsequent progress in drug development has

Table 3. Multivariable Analysis for Overall Survival

Covariate	Level	n	HR (95% CI)	HR *p* Value
ICI	Yes	52	0.67 (0.49-0.93)	**0.018**
	No	305	REF	
Chemotherapy	Yes	192	0.59 (0.45-0.77)	**<0.001**
	No	165	REF	
Brain metastasis	Yes	107	1.16 (0.91-1.48)	0.233
	No	250	REF	
Targeted therapy	Yes	43	0.52 (0.36-0.74)	**<0.001**
	No	314	REF	
Surgery	Yes	85	0.56 (0.43-0.74)	**<0.001**
	No	272	REF	
Sex	Female	191	1.47 (1.18-1.84)	**<0.001**
	Male	166	REF	
Race	American Indian or Alaska Native	1	8.34 (1.09-64.14)	**0.040**
	Asian	11	1.09 (0.53-2.21)	0.819
	Black	32	0.62 (0.42-0.91)	**0.016**
	Other race	36	1.41 (0.92-2.16)	0.114
	Unknown	52	0.84 (0.54-1.29)	0.422
	White	225	REF	
Ethnicity	Hispanic or Latino	7	0.85 (0.37-1.94)	0.692
	Unknown	63	1.08 (0.77-1.54)	0.672
	Not Hispanic or Latino	287	REF	
U.S. Region	Unknown	45	0.78 (0.50-1.23)	0.289
	Northeast region	72	1.10 (0.81-1.49)	0.556
	Midwest region	104	0.62 (0.46-0.85)	**0.003**
	South Region	136	REF	
Stage	3	72	0.61 (0.47-0.81)	**<0.001**
	2	21	0.45 (0.27-0.75)	**0.002**
	1	24	0.29 (0.18-0.47)	**<0.001**
	Unknown	18	0.53 (0.32-0.89)	**0.016**
	4	222	REF	

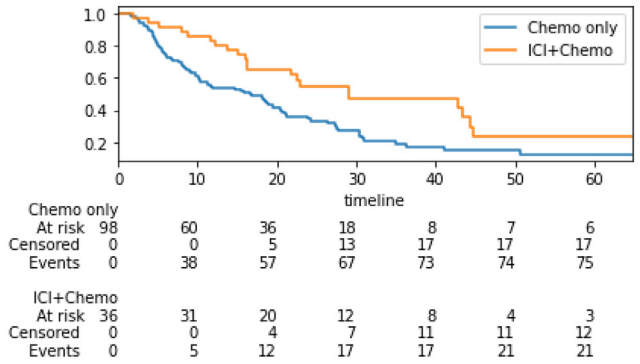
CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; REF, reference.

resulted in improved survival for a subset of patients with stage 4 disease. However, robust therapeutic benefits were limited to patients with the common EGFR-activating mutations. Patients with EGFR ex20ins represent a distinct subset of lung adenocarcinoma that does not respond to standard TKIs; this has been attributed to the restricted size of the adenosine triphosphate–binding pocket.[19] Until recently, platinum-



Stage group	Level	N	Median survival time(month)	Logrank test P-value
stage 4	ICI (ICI only or combined with chemotherapy)	39	29.0(19.3,44.3)	<0.005
	No ICI	183	14.6(10.1,18.4)	

Figure 1. Stage 4 patients treated with ICI versus no ICI. ICI, immune checkpoint inhibitors.

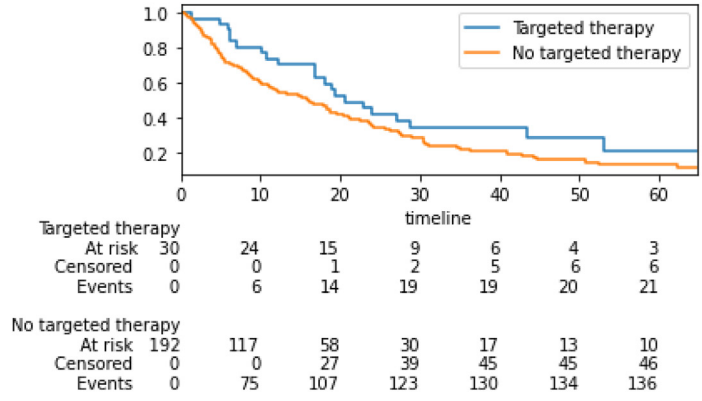


Stage group	Level	N	Median survival time(month)	Logrank test P-value
stage 4	Chemotherapy only	98	16.5(10.1,20.3)	0.01
	ICI+Chemotherapy	36	29.1(16.3,44.3)	

Figure 2. Stage 4 patients treated with ICI plus Chemo versus Chemo only. Chemo, chemotherapy; ICI, immune checkpoint inhibitors.

based chemotherapy has remained the mainstay of treatment for this patient subset. The role of ICI for this patient population has not been sufficiently delineated and several novel TKIs specific to ex20ins are currently under development.

Our analysis of the ASCO CancerLinQ database provides interesting insights into the overall outcomes for the EGFR ex20ins patient population and outcomes with various systemic therapy outcomes. The overall median survival for stage 4 patients at approximately 16 months is much lower than the outcomes reported for the common EGFR mutation and other driver mutations such as *ALK* gene rearrangement.[20,21] Because these data were obtained at a period during which amivantamab and mobocertinib were not available, they could serve as a benchmark to measure future progress with novel approaches. Another observation is the proportion of patients with brain metastasis in patients with EGFR ex20ins–mutated patients is higher than that in patients without driver mutations and comparable to those in patients with common EGFR mutation. We also found intriguing observations related to the role of ICI, which is in contrast with previous reports. In patients with the common EGFR mutation, the role of ICI has been disappointing with a response rate less than 5%.[22] Consequently, checkpoint inhibitors are not recommended as monotherapy even in the post-TKI acquired resistance setting. However, post hoc analysis of the IMPower 150 study suggested potential benefits for the combination of chemotherapy, bevacizumab and atezolizumab in the EGFR-mutated patient population.[23] A recent trial of nivolumab in combination with chemotherapy failed to



Stage group	Level	N	Median survival time(month)	Logrank test P-value
stage 4	Targeted therapy	30	20.6(16.8,43.3)	0.03
	No targeted therapy	192	16.1(11.2,19.3)	

Figure 3. Stage 4 patients treated with targeted therapy.

Table 4. Univariate Analysis for Overall Survival in Stage 4 Patients

Covariate	Level	n	HR (95% CI)	HR *p* Value
ICI	Yes	39	0.78 (0.55–1.11)	0.163
	No	183	REF	
Chemotherapy	Yes	134	1.28 (0.39–4.21)	0.682
	No	88	REF	
Brain metastasis	Yes	81	0.89 (0.68–1.17)	0.410
	No	141	REF	
Targeted therapy	Yes	30	1.05 (0.71–1.54)	0.816
	No	192	REF	
Surgery	Yes	33	1.06 (0.73–1.53)	0.771
	No	189	REF	
Sex	Female	114	1 (0.77–1.3)	0.982
	Male	108	REF	
Race	American Indian or Alaska Native	1	6.54 (0.89–48.02)	0.065
	Asian	6	2.02 (0.89–4.61)	0.094
	Black or African American	20	1.23 (0.77–1.97)	0.391
	Other Race	24	0.97 (0.63–1.5)	0.889
	Unknown	30	0.86 (0.58–1.29)	0.473
	White	141	REF	
Ethnicity	Hispanic or Latino	5	0.54 (0.22–1.32)	0.178
	Unknown	38	1.09 (0.76–1.54)	0.646
	Not Hispanic or Latino	179	REF	
Region	Unknown	25	1.14 (0.73–1.78)	0.570
	Northeast Region	39	1.37 (0.94–2)	0.103
	Midwest Region	66	1.4 (1.01–1.92)	0.040
	South Region	92	REF	

CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; REF, reference.

Table 5. Multivariable Analysis for Overall Survival in Stage 4 Patients

Covariate	Level	n	HR (95% CI)	HR *p* Value
ICI	Yes	39	0.65 (0.45–0.95)	**0.026**
	No	183	REF	
Chemotherapy	Yes	134	0.54 (0.38–0.76)	**<0.001**
	No	88	REF	
Brain metastasis	Yes	81	1.15 (0.85–1.56)	0.351
	No	141	REF	
Targeted therapy	Yes	30	0.40 (0.24–0.65)	**<0.001**
	No	192	REF	
Surgery	Yes	33	0.52 (0.35–0.78)	**0.001**
	No	189	REF	
Sex	Female	114	1.46 (1.09–1.95)	**0.012**
	Male	108	REF	
Race	American Indian or Alaska Native	1	6.53 (0.82–52.11)	0.076
	Asian	6	0.98 (0.38–2.52)	0.973
	Black or African American	20	0.55 (0.34–0.92)	**0.021**
	Other race	24	1.14 (0.66–1.98)	0.632
	Unknown	30	0.75 (0.43–1.29)	0.292
	White	141	REF	
Ethnicity	Hispanic or Latino	5	1.28 (0.43–3.80)	0.659
	Unknown	38	1.31 (0.84–2.07)	0.238
	Not Hispanic or Latino	179	REF	
Region	Unknown	25	0.75 (0.42–1.32)	0.320
	Northeast region	39	1.09 (0.72–1.64)	0.697
	Midwest region	66	0.66 (0.43–0.99)	**0.046**
	South region	92	REF	

CI, confidence interval; HR, hazard ratio; ICI, immune checkpoint inhibitor; REF, reference.

exhibit improved outcomes over chemotherapy alone for patients with EGFR mutation.[24] Our analysis noted a favorable effect with the combination of immunotherapy with chemotherapy for patients with EGFR ex20ins. However, our results could be strongly biased by patient selection. It is entirely possible that patients with more indolent disease received more lines of therapy that included immunotherapy compared with those with aggressive disease biology.

The finding related to improved outcomes with the targeted therapies used for the patient population in this database is relatively modest and consistent with previous reports; a recent study by ECOG-ACRIN (EA5162) and the POSITION20 trial found modest anticancer activity with osimertinib.[25,26] This trial is now being expanded to include more patients to substantiate the early findings. A number of newer targeted therapies specific to ex20ins have noted a higher response rate of nearly 40% with acceptable tolerability profiles. Amivantamab and mobocertinib have noted response rates of 40% and 25% respectively and are presently in clinical use. However, the median progression-free survival with these two agents is relatively modest at approximately 7 months.[27,28]

Our analysis is not without limitations; molecular testing is still underperformed, and it is likely that not all patients with EGFR ex20ins were captured for the period included in this analysis. It is also possible that centers that used targeted testing panels that did not include EGFR ex20ins would not have detected the mutation. The database includes retrospectively collected data from the medical records of multiple facilities in the country and is limited in the information it provides. As with any post hoc analysis, we do not know the specific reasons that guided various treatment choices adopted for patients; this limits our ability to attribute outcomes to the specific intervention. Because of these limitations, as with any real-world data sets, we were unable to perform analyses at a more granular level for treatment efficacy using many possible confounding factors. The smaller size of the cohort and missing information for many patients limited our ability to analyze for outcomes such as progression-free survival and response. In addition, this database, being based in the United States, may not fully describe the characteristics of this disease in other patient populations in the rest of the world. Despite these limitations, for smaller subsets of lung adenocarcinoma, population-level data such as from the ASCO CancerLinQ database may provide the best information to guide research and patient care. We also note that the number of patients in the EGFR ex20ins included in this analysis makes this one of the largest data sets.

In summary, EGFR ex20ins mutation represents a distinct clinical challenge in patients with NSCLC; novel treatment options are urgently needed to improve patient outcomes.

CRediT Authorship Contribution Statement

Madhusmita Behera: Conceptualization, Investigation, Methodology, Supervision, Writing- original draft preparation.

Renjian Jiang: Methodology, Data curation, Formal analysis, Writing-reviewing and editing.

Zhonglu Huang: Methodology, Data curation, Formal analysis, Writing- reviewing and editing.

Becky Bunn: Project administration, Funding acquisition, Writing- reviewing and editing.

Murry W. Wynes: Project administration, Funding acquisition, Writing- reviewing and editing.

Jeffrey Switchenko: Methodology, Writing- reviewing and editing.

Giorgio Scagliotti: Conceptualization, Writing-reviewing and editing.

Chandra P. Belani: Conceptualization, Writing-reviewing and editing.

Suresh S. Ramalingam: Conceptualization, Investigation, Supervision, Writing- reviewing and editing.

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References

1. Howlader N, Forjaz G, Mooradian MJ, et al. The effect of advances in lung-cancer treatment on population mortality. *N Engl J Med*. 2020;383:640–649.
2. Zhang T, Wan B, Zhao Y, et al. Treatment of uncommon EGFR mutations in non-small cell lung cancer: new evidence and treatment. *Transl Lung Cancer Res*. 2019;8:302–316.
3. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12:735–742.
4. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with

metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol*. 2013;31:3327–3334.
5. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer - molecular and clinical predictors of outcome. *N Engl J Med*. 2005;353:133–144.
6. Hirsch FR, Varella-Garcia M, Bunn PA Jr, et al. Molecular predictors of outcome with gefitinib in a phase III placebo-controlled study in advanced non-small-cell lung cancer. *J Clin Oncol*. 2006;24:5034–5042.
7. Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2014;15:213–222.
8. Greulich H, Chen TH, Feng W, et al. Oncogenic transformation by inhibitor-sensitive and -resistant EGFR mutants. *PLoS Med*. 2005;2:e313.
9. Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. *Lancet Oncol*. 2012;13:e23–e31.
10. Oxnard GR, Lo PC, Nishino M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. *J Thorac Oncol*. 2013;8:179–184.
11. Harada T, Lopez-Chavez A, Xi L, Raffeld M, Wang Y, Giaccone G. Characterization of epidermal growth factor receptor mutations in non-small-cell lung cancer patients of African-American ancestry. *Oncogene*. 2011;30:1744–1752.
12. Arcila ME, Nafa K, Chaft JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol Cancer Ther*. 2013;12:220–229.
13. Imran M, Khan SA, Alshammari MK, et al. Discovery, development, inventions, and patent trends on mobocertinib succinate: the first-in-class oral treatment for NSCLC with EGFR Exon 20 insertions. *Biomedicines*. 2021;9:1938.
14. Beau-Faller M, Prim N, Ruppert AM, et al. Rare EGFR exon 18 and exon 20 mutations in non-small-cell lung cancer on 10 117 patients: a multicentre observational study by the French ERMETIC-IFCT network. *Ann Oncol*. 2014;25:126–131.
15. Yang JC, Sequist LV, Geater SL, et al. Clinical activity of afatinib in patients with advanced non-small-cell lung cancer harbouring uncommon EGFR mutations: a combined post-hoc analysis of LUX-Lung 2, LUX-Lung 3, and LUX-Lung 6. *Lancet Oncol*. 2015;16:830–838.
16. Piotrowska Z, Wang Y, Sequist LV, Ramalingam SS. ECOG-ACRIN 5162: a phase II study of osimertinib 160 mg in NSCLC with EGFR exon 20 insertions. *J Clin Oncol*. 2020;38(suppl 15):9513–9513.
17. Potter D, Brothers R, Kolacevski A, et al. Development of CancerLinQ, a health information learning platform from multiple electronic health record systems to support improved quality of care. *JCO Clin Cancer Inform*. 2020;4:929–937.
18. Potter DM, Riffon MF, Manning B, et al. Summary of the 12 most common cancers in the CancerLinQ Discovery (CLQD) database. *JCO Clin Cancer Inform*. 2021;5:658–667.
19. Robichaux JP, Elamin YY, Tan Z, et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. *Nat Med*. 2018;24:638–646.
20. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med*. 2020;382:41–50.
21. Pacheco JM, Gao D, Smith D, et al. Natural history and factors associated with overall survival in Stage IV ALK-rearranged non-small cell lung cancer. *J Thorac Oncol*. 2019;14:691–700.
22. Lee CK, Man J, Lord S, et al. Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer-a meta-analysis. *J Thorac Oncol*. 2017;12:403–407.
23. Reck M, Mok TSK, Nishio M, et al. Atezolizumab plus bevacizumab and chemotherapy in non-small-cell lung cancer (IMpower150): key subgroup analyses of patients with EGFR mutations or baseline liver metastases in a randomised, open-label phase 3 trial. *Lancet Respir Med*. 2019;7:387–401.
24. Mok TSK, Nakagawa K, Park K, et al. Nivolumab (NIVO) + chemotherapy vs chemotherapy in patients (pts) with EGFR-mutated metastatic non-small cell lung cancer (mNSCLC) with disease progression after EGFR tyrosine kinase inhibitors (TKIs) in CheckMate 722. *Ann Oncol*. 2022;33(suppl 9):S1561–S1562.
25. Piotrowska Z, Hata AN. Resistance to first-line osimertinib in EGFR-mutant NSCLC: tissue is the issue. *Clin Cancer Res*. 2020;26:2441–2443.
26. Zwierenga F, van Veggel B, Hendriks LEL, et al. High dose osimertinib in patients with advanced stage EGFR exon 20 mutation-positive NSCLC: results from the phase 2 multicenter POSITION20 trial. *Lung Cancer*. 2022;170:133–140.
27. Zhou C, Ramalingam SS, Kim TM, et al. Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with EGFR Exon 20 insertion-positive metastatic non-small cell lung cancer: A Phase 1/2 open-label nonrandomized clinical trial. *JAMA Oncol*. 2021;7:e214761.
28. Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR Exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the CHRYSALIS Phase I study. *J Clin Oncol*. 2021;39:3391–3402.