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Prognostic Value of *EGFR* Exon-20 Insertions in Czech Patients With Advanced Non-small Cell Lung Cancer

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Abstract. *Background/Aim: Per literature, patients with epidermal growth factor receptor (EGFR) exon-20 insertions respond poorly to tyrosine kinase inhibitors (TKIs). This study analyzed real-world data to examine the prognostic and predictive value of these mutations. Patients and Methods: We conducted a retrospective cohort study using Czech TULUNG Registry data, with data on multiple mutation types, collected in 2011-2020. Results: We analyzed 554 (95.85%) patients with EGFR exon-19 deletions or exon-21 L858R substitutions and 24 (4.15%) patients with exon-20 insertions who received first-line high-value therapies. We summarized clinical characteristics and outcomes in all patients and by cohort. The risk of progression was statistically significantly higher (86%) in the exon-20 insertion cohort compared to the cohort with other mutations. Although not statistically significant, the risk of death was 44% higher in patients with exon-20 insertions. Conclusion: Advanced NSCLC patients with rare EGFR exon-20 insertions have a high risk of progression.*

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Generally, epidermal growth factor receptor (EGFR) activating mutations are detected in approximately 10-15% of patients with non-squamous non-small cell lung cancer (NSCLC). In Asia, the prevalence is much higher, being found in about 30-50% of patients (1). Approximately 85% of primary *EGFR* mutations are exon-19 deletions and exon-21 L858R substitutions (common *EGFR* mutations), which are associated with sensitivity to tyrosine kinase inhibitors (TKIs) and with a favorable overall survival. About 5-12% of primary *EGFR* mutations are exon-20 insertions (2).

Databases and registries that have information on patients with rare mutations are scarce. Literature review showed

very few studies examining the prognostic value of exon-20 insertions (2, 3). Most of these studies included less than 30 patients with exon-20 insertions and patients' lines of therapy were mixed. Preliminary evidence suggests that patients with exon-20 insertions have a worse overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) compared to patients with other *EGFR* mutations, *e.g.*, exon-19 deletions, exon-21 L858R substitutions, and *EGFR* wildtype mutations, across different therapies and treatment lines (4-8). More data and further analyses are needed to quantify the prognostic value of exon-20 insertions.

Likewise, the predictive value for treatment with TKI therapies in exon-20 insertion patients is not well understood. Literature provides increasing evidence that patients with exon-20 insertions do not respond well to TKIs (2, 8, 9) and some authors suggest association with poor responses (10).

Hence, further research is needed to understand the prognostic and predictive value of exon-20 insertions compared to common *EGFR* mutations. The aim of our study was to analyze data from a high-quality disease registry and attempt to answer these research questions. The TULUNG Registry is a non-interventional post-registration database focused on collecting epidemiological and clinical data in patients with NSCLC who have been treated with high-value therapies. The project was initiated in July 2011 by the Czech Society for Oncology. It is one of a few registries that includes data on rare mutations in NSCLC patients.

Patients and Methods

This is a retrospective cohort study based on data collected between 2011-2020 in the Czech Lung Cancer (TULUNG) Registry to evaluate prognostic values of exon-20 insertions in patients with advanced NSCLC. This registry includes exclusively patients who received so-called high-value or targeted therapies in the Czech Republic, *i.e.*, afatinib (Giotrif), alectinib (Alecensa), atezolizumab (Tecentriq), bevacizumab (Avastin), ceritinib (Zykadia), crizotinib (Xalkori), dabrafenib (Tafinlar), durvalumab (Imfinzi), erlotinib (Tarceva), gefitinib (Iressa), lorlatinib (Lorviqua), nintedanib (Vargatef), nivolumab (Opdivo), osimertinib (Tagrisso), pembrolizumab (Keytruda), pemetrexed (Alimta), trametinib (Mekinist). The listed drugs are known to be used more often in patients with common mutations as they are reportedly effective (11, 12).

Confidentiality of patient records was maintained throughout the study. All study reports contained aggregated data only and did not identify individual patients or physicians.

Inclusion criteria. Male and female adult patients (aged ≥18 years) with a confirmed advanced NSCLC treated with high-value therapeutic agents who signed informed consent to be included in the registry. The number of patients was not predetermined or limited.

Exclusion criteria. Patients who did not sign an informed consent to provide their medical data to the TULUNG Registry.

Study objectives. The primary objective was to demonstrate the prognostic value of exon-20 insertions compared to common *EGFR* mutations measured by OS, PFS, and time to next treatment (TTNT).

The secondary objective was to describe the real-world patient characteristics, treatment patterns, and clinical outcomes in advanced NSCLC patients with exon- 20 insertions.

Methods. We analyzed clean and validated data of NSCLC patients treated with high-value therapies. Patients who did not have valid information on any of the following characteristics – date of birth, gender, smoking status, line of therapy, the Eastern Cooperative Oncology Group Performance Status (ECOG PS), TNM classification, stage of primary carcinoma, histology and/or cytology type of carcinoma, date of diagnosis, date of treatment initiation, and patient status – were excluded from the analysis. Data from centers that did not consent to use their data were excluded as well. We examined two cohorts of patients, the Exon-20 insertion cohort, and the Exon-19 deletion/Exon-21 L858R substitution (common mutation) cohort. The index date was defined as the start date of the first high-value therapy during the study period, since patients are entered in the registry once they receive their first high-value therapy and not when they are diagnosed. Patients had to have a positive test for the mutation before or up to 30 days after the index date. Per protocol, patients belonging to both cohorts were excluded.

For better comparisons, we narrowed the population analyzed for clinical outcomes to those patients who received a high-value therapy in a confirmed overall first-line. Time-to-event analyses were restricted to these narrowed populations in both cohorts.

We used descriptive statistics for patient disposition, characterized for both all eligible patients and a narrowed population of patients with a confirmed first-line high-value therapy. Demographic and disease characteristics of patients were summarized. Continuous parameters were described using the mean with a standard deviation (SD) and the median with the minimum and maximum value, together with the total number of observations. Categorical parameters were summarized using absolute and relative frequencies. Relative frequencies were calculated based on the number of patients in the relevant cohort. A comparison of continuous parameters was performed using the Mann-Whitney *U*-test, while categorical parameters were analyzed using the Fisher's exact test.

OS, PFS, and TTNT were calculated in the narrowed population.

OS was defined as the time from the index date to the date of death from any cause. If a patient was still alive, we censored the data at the time of the last follow-up defined as the date of the last structured activity (most recent visit, treatment start/end, date of progression). PFS was defined as the time from the index date to the date of death, the start date of the next line of therapy, or the date of progression, whichever occurred first. If a patient did not reach the event, the data were censored, the censoring time being the date of the last follow-up, which was defined in the same manner as for OS. OS and PFS were estimated using the Kaplan–Meier method and all point estimates included 95% confidence intervals (95%CI). Differences in OS and PFS between the cohorts were tested using the log-rank test.

TTNT was defined as time to subsequent high-value therapy or death, whichever occurred first. As these are competing risks, they were analyzed and visualized using a cumulative incidence function. Differences in TTNT between cohorts were tested using the Gray test.

To analyze treatment patterns, we evaluated treatment sequences regardless of their duration. As the registry includes only those

Table I. *Disposition of patients – all eligible patients*.

	All (N=698)	Exon-20 insertions (N=28)	Common mutations (N=670)	*p*-Value
Age (at index date) [years]				
N	698	28	670	0.980
Mean (SD)	65.4 (11.3)	65.8 (8.5)	65.4 (11.4)	
Median (Min-Max)	66.8 (23.7-89.8)	69.1 (49.2-80.3)	66.8 (23.7-89.8)	
Gender, n (%)				
N	698	28	670	>0.999
Man	235 (33.7%)	9 (32.1%)	226 (33.7%)	
Woman	463 (66.3%)	19 (67.9%)	444 (66.3%)	
Smoking status, n (%)				
N	698	28	670	0.294
Non-smoker	400 (57.3%)	14 (50.0%)	386 (57.6%)	
Former smoker (one year before diagnosis)	176 (25.2%)	6 (21.4%)	170 (25.4%)	
Smoker	122 (17.5%)	8 (28.6%)	114 (17.0%)	
ECOG PS (at start of therapy), n (%)				
N	698	28	670	0.958
0	145 (20.8%)	5 (17.9%)	140 (20.9%)	
1	486 (69.6%)	21 (75.0%)	465 (69.4%)	
2	63 (9.0%)	2 (7.1%)	61 (9.1%)	
3	4 (0.6%)	0 (0.0%)	4 (0.6%)	
Histology, n (%)				
N	698	28	670	0.509
Adenocarcinoma	640 (91.7%)	26 (92.9%)	614 (91.6%)	
Squamous cell carcinoma	24 (3.4%)	0 (0.0%)	24 (3.6%)	
Adenosquamous cell carcinoma	8 (1.1%)	0 (0.0%)	8 (1.2%)	
Other type of carcinoma	3 (0.4%)	0 (0.0%)	3 (0.4%)	
Non-specified	23 (3.3%)	2 (7.1%)	21 (3.1%)	
Clinical stage of primary carcinoma at time of diagnosis, n (%)				
N	695	28	667	0.521
IA	20 (2.9%)	1 (3.6%)	19 (2.8%)	
IB	13 (1.9%)	1 (3.6%)	12 (1.8%)	
IIA	21 (3.0%)	0 (0.0%)	21 (3.1%)	
IIB	8 (1.2%)	1 (3.6%)	7 (1.0%)	
IIIA	40 (5.8%)	2 (7.1%)	38 (5.7%)	
IIIB	72 (10.4%)	4 (14.3%)	68 (10.2%)	
IIIC (valid from TNM8)	1 (0.1%)	0 (0.0%)	1 (0.1%)	
IV	463 (66.6%)	18 (64.3%)	445 (66.7%)	
IVA (valid from TNM8)	22 (3.2%)	1 (3.6%)	21 (3.1%)	
IVB (valid from TNM8)	35 (5.0%)	0 (0.0%)	35 (5.2%)	
Resistance mutations*, n (%)				
N	698	28	670	0.165
Proved	63 (9.0%)	0 (0.0%)	63 (9.4%)	
Not proved	635 (91.0%)	28 (100.0%)	607 (90.6%)	
ALK translocation, n (%)				
N	294	12	282	0.655
Proved	3 (1.0%)	0 (0.0%)	3 (1.1%)	
Not proved	269 (91.5%)	12 (100.0%)	257 (91.1%)	
Unable to determine	22 (7.5%)	0 (0.0%)	22 (7.8%)	
KRAS mutation, n (%)				
N	93	2	91	>0.999
Proved	6 (6.5%)	0 (0.0%)	6 (6.6%)	
Not proved	86 (92.5%)	2 (100.0%)	84 (92.3%)	
Unable to determine	1 (1.1%)	0 (0.0%)	1 (1.1%)	
PD-L1 status, n (%)				
N	65	3	62	0.269
Positive	31 (47.7%)	0 (0.0%)	31 (50.0%)	
Negative	30 (46.2%)	3 (100.0%)	27 (43.5%)	
Unable to determine	4 (6.2%)	0 (0.0%)	4 (6.5%)	

*Resistance mutation means T790M and/or C-MET specification.

Table II. *Disposition of patients – narrowed population.*

	All (N=578)	Exon 20 insertions (N=24)	Common mutations (N=554)	*p*-Value
Age (at index date) [years]				
N	578	24	554	0.282
Mean (SD)	65.8 (11.6)	64.3 (8.1)	65.8 (11.7)	
Median (Min–Max)	67.4 (23.7–89.8)	63.8 (49.2–75.5)	67.5 (23.7–89.8)	
Gender, n (%)				
N	578	24	554	0.825
Man	182 (31.5%)	8 (33.3%)	174 (31.4%)	
Woman	396 (68.5%)	16 (66.7%)	380 (68.6%)	
Smoking status, n (%)				
N	578	24	554	0.146
Non-smoker	331 (57.3%)	11 (45.8%)	320 (57.8%)	
Former smoker (one year before diagnosis)	145 (25.1%)	5 (20.8%)	140 (25.3%)	
Smoker	102 (17.6%)	8 (33.3%)	94 (17.0%)	
ECOG PS (at start of therapy), n (%)				
N	578	24	554	0.490
0	130 (22.5%)	5 (20.8%)	125 (22.6%)	
1	399 (69.0%)	19 (79.2%)	380 (68.6%)	
2	45 (7.8%)	0 (0.0%)	45 (8.1%)	
3	4 (0.7%)	0 (0.0%)	4 (0.7%)	
Histology, n (%)				
N	578	24	554	0.427
Adenocarcinoma	552 (95.5%)	22 (91.7%)	530 (95.7%)	
Squamous cell carcinoma	4 (0.7%)	0 (0.0%)	4 (0.7%)	
Adenosquamous cell carcinoma	4 (0.7%)	0 (0.0%)	4 (0.7%)	
Other type of carcinoma	1 (0.2%)	0 (0.0%)	1 (0.2%)	
Non-specified	17 (2.9%)	2 (8.3%)	15 (2.7%)	
Clinical stage of primary carcinoma at time of diagnosis, n (%)				
N	577	24	553	0.238
IA	18 (3.1%)	1 (4.2%)	17 (3.1%)	
IB	9 (1.6%)	1 (4.2%)	8 (1.4%)	
IIA	16 (2.8%)	0 (0.0%)	16 (2.9%)	
IIB	4 (0.7%)	1 (4.2%)	3 (0.5%)	
IIIA	28 (4.9%)	2 (8.3%)	26 (4.7%)	
IIIB	51 (8.8%)	3 (12.5%)	48 (8.7%)	
IIIC (valid from TNM8)	1 (0.2%)	0 (0.0%)	1 (0.2%)	
IV	393 (68.1%)	15 (62.5%)	378 (68.4%)	
IVA (valid from TNM8)	22 (3.8%)	1 (4.2%)	21 (3.8%)	
IVB (valid from TNM8)	35 (6.1%)	0 (0.0%)	35 (6.3%)	
Resistance mutations*, n (%)				
N	578	24	554	0.097
Proved	61 (10.6%)	0 (0.0%)	61 (11.0%)	
Not proved	517 (89.4%)	24 (100.0%)	493 (89.0%)	

*Resistance mutation means T790M and/or C-MET specification.

medications labelled as high-value therapies, the first line of treatment was the first prescription of such therapy and not necessarily the first overall treatment. Hazard ratios were obtained from non-adjusted Cox proportional hazards models for OS and PFS, and from the Fine-Gray model for TTNT.

Results

We analyzed a total of 698 patients fulfilling the eligibility criteria in this real-world disease registry. Out of these patients, 670 (95.99%) had exon-19 deletion and/or exon-21 L858R substitution, while 28 (4.01%) had exon-20 insertions. The narrowed population included 554 (95.85%) patients with common mutations and 24 (4.15%) patients with exon-20 insertions. We covered 975.66 patient-years for common mutations and 28.87 patient-years for exon-20 insertions counted from the first high-value therapy. In all eligible patients and in the narrowed population, we described both cohorts separately as well as the whole population using descriptive statistics for patient disposition at index date (Table I and Table II). We did not find any statistically significant

differences between the two mutation cohorts in baseline characteristics, such as demographics, smoking status, ECOG PS, histology, and TNM stage. Only a small proportion of all eligible patients had information on *ALK, KRAS*, and *PD-L1* mutations. The ALK translocation was tested in 272 (38.97%) patients, the *KRAS* mutation in 92 (13.18%) patients, and the *PD-L1* mutation in 61 (8.74%) patients in the total population; patient numbers per cohort are shown in Table I.

In all eligible patients, we summarized treatment patterns in the exon-20 insertion and common mutation cohorts (Table III and Table IV), and stratified the patients based on age and type of the first high-value therapy disregarding the therapy line (Table V and Table VI). In the common mutation cohort, patients received pemetrexed (N=34), bevacizumab (N=3), afatinib (N=179), durvalumab (N=1), gefitinib (N=315), and erlotinib (N=138). In the exon-20 insertion cohort, patients received pemetrexed (N=10), bevacizumab (N=2), afatinib (N=6), gefitinib (N=8), and erlotinib (N=2). In the common mutation cohort, 8% patients were treated with osimertinib, while no patient received osimertinib in the exon-20 insertion cohort (Table VII). The median age when patients received a high-value therapy differed in both cohorts and per therapy type. All patients with common mutations were in their sixties when they received their first high-value therapy. Patients with exon-20 insertions were mostly in their seventies, except for those who received bevacizumab and gefitinib, these patients were in their fifties.

The proportion of patients who received a high-value therapy in their overall first line, *i.e.*, those who are included in the narrowed patient populations, is almost equal in both cohorts, namely, 554 (82.7%) patients received a first-line high-value therapy in the common mutation cohort and 24 (85.7%) patients received a first-line high-value therapy in the exon-20 insertion cohort.

For the narrowed population, we summarized clinical outcomes (PFS, OS, and TTNT) in all patients and in both cohorts (Table VIII, Figure 1, Figure 2, Figure 3). We observed that the PFS was statistically significantly (p=0.007) lower in patients with exon-20 insertions compared to those with common mutations, and the difference between the median PFS was 4.1 months. We did not find any statistically significant differences in the OS and TTNT, however, the estimates were highly variable due to the low number of patients in the exon-20 insertion cohort. We summarize the results of the Cox and Fine-Gray models in Table IX.

Table III. *Sequences of high-value therapies in patients with exon-20 insertions.*

1st line	2nd line	3rd line	N (%)
Gefitinib			7 (25.0%)
Pemetrexed			3 (10.7%)
Pemetrexed	Erlotinib		2 (7.1%)
Afatinib			2 (7.1%)
Afatinib	Pemetrexed		2 (7.1%)
Afatinib	Pemetrexed	Erlotinib	2 (7.1%)
	Pemetrexed	Erlotinib	2 (7.1%)

Note: An empty cell in the table indicates a line without record of any high-value therapy. Treatment sequence was evaluated regardless of treatment duration. The sequence may not be final for patients who are alive and continue treatment. The table includes only treatments prescribed to at least two patients.

Table IV. *Sequences of high-value therapies in patients with common mutations.*

1st line	2nd line	3rd line	N (%)
Gefitinib			201 (30.0%)
Afatinib			112 (16.7%)
	Erlotinib		68 (10.1%)
Gefitinib	Pemetrexed		56 (8.4%)
Erlotinib			39 (5.8%)
Afatinib	Pemetrexed		19 (2.8%)
Gefitinib	Osimertinib		15 (2.2%)
Afatinib	Osimertinib		13 (1.9%)
Pemetrexed	Erlotinib		11 (1.6%)
Gefitinib	Pemetrexed	Erlotinib	9 (1.3%)
Erlotinib	Pemetrexed		9 (1.3%)
Afatinib	Pemetrexed	Erlotinib	7 (1.0%)
	Gefitinib		7 (1.0%)
	Erlotinib	Pemetrexed	7 (1.0%)
Afatinib	Erlotinib		6 (0.9%)
	Pemetrexed	Erlotinib	6 (0.9%)
		Erlotinib	6 (0.9%)

Note: An empty cell in the table indicates a line without record of any high-value therapy. Treatment sequence was evaluated regardless of treatment duration. The sequence may not be final for patients who are alive and continue treatment. The table includes only treatments prescribed to at least six patients.

Discussion

We observed that patients with exon-20 insertions had a statistically significantly worse real-world PFS hazard ratio (HR=1.86, 95%CI=1.17-2.95, p=0.007) with the risk of progression being 86% higher compared to that of patients with common mutations. Although not statistically significant, patients with exon-20 insertions had a worse OS (HR=1.44, 95%CI=0.79-2.64, p=0.232) with the risk of death being 44% higher compared to patients with common mutations. Patients with exon-20 insertions had a median PFS of about 4 months and a median OS almost 6 months shorter than that of patients with common mutations.

The results of our analyses, namely, PFS HR=1.86, OS HR=1.44, TTNT HR=1.46, are consistent with the results of

Table V. *Age distribution in exon-20 insertion cohort stratified by the first high-value therapy.*

	Pemetrexed (N=10)	Bevacizumab (N=2)	Afatinib (N=6)	Gefitinib (N=8)	Erlotinib (N=2)
Age (at index date) [years]					
N	10	2	6	8	2
Mean (SD)	68.0 (6.3)	51.0 (2.5)	72.5 (2.9)	59.5 (5.9)	75.2 (7.2)
Median (Min-Max)	70.8 (56.4-76.0)	51.0 (49.2-52.8)	72.8 (68.9-75.5)	59.2 (50.7-69.4)	75.2 (70.2-80.3)

SD: Standard deviation.

Table VI. *Age distribution in common mutation cohort stratified by the first high-value therapy.*

	Pemetrexed (N=34)	Bevacizumab (N=3)	Afatinib (N=179)	Durvalumab (N=1)	Gefitinib (N=315)	Erlotinib (N=138)
Age (at index date) [years]						
N	34	3	179	1	315	138
Mean (SD)	62.8 (11.6)	57.2 (12.8)	62.0 (11.5)	-	68.2 (11.2)	64.1 (10.4)
Median (Min-Max)	63.9 (40.9-86.8)	64.2 (42.4-64.9)	64.9 (23.7-86.3)	61.3 (–)	69.9 (34.7-89.8)	65.1 (33.1-83.3)

SD: Standard deviation.

the analyses from other databases, *e.g.*, the Flatiron Health™ data, that show PFS HR=1.72, OS HR=1.87, and TTNT HR=1.57 (3).

In most studies, the start date for time-to-event outcomes was the time of diagnosis or the start of the overall first-line therapy. We found this approach non-feasible due to the fact that the date of diagnosis was missing for a large proportion of patients in the dataset, hence, in our study, the start date was generally later, since patients might have had other treatment lines prior to the first high-value therapy. While we cannot ascertain it for all patients due to missing data, we expect the index date is after the date of diagnosis in the exon-20 insertion cohort, hence, the patients were in a more advanced disease stage when they received the first high-value therapy. Also, the treatment sequences were different. Osimertinib was prescribed to patients with common mutations only.

Our patients were older and in a more advanced stage of disease compared to patients analyzed in other countries, *e.g.*, in Japan. In Maemondo *et al.*'s study from 2010, the median age of the patients was 64 years with the oldest patient being 75 years old, while the median age of our patients was 67 years with the oldest patient being 90 years old (12). The ECOG PS was lower in the Japanese patients (0 in 49% of patients, 1 in 52% of patients, 2 in 1% of patients) compared to our population (0 in 22.5% of patients, 1 in 69% of patients, 2 in 7.8% of patients, 3 in 0.7% of patients). Sixty-six percent of the Japanese patients were non-smokers, while non-smokers represented 57% of our patients. The reason for the Czech patients being older and more frail is that high-value therapies are prescribed exclusively to patients with advanced disease, disregarding their age and line of treatment.

Table VII. *Number of patients treated with osimertinib.*

	All (N=698)	Exon-20 insertions (N=28)	Common mutations (N=670)
Treated with osimertinib	56 (8.0%)	0 (0.0%)	56 (8.4%)

In 2020, Brat *et al.* published an article on real-world effectiveness of first-line anticancer treatments in stage IIIB/IV NSCLC patients based on an analysis of data from the TULUNG Registry (13). Without stratifying patients per types of mutations, they observed that the median OS was 23 months for erlotinib, 29.3 months for afatinib, 19.6 months for gefitinib, 12.2 months for pemetrexed, 17.5 months for pemetrexed maintenance, 15.8 months for bevacizumab, and 15.8 months for bevacizumab maintenance. The authors stated that the OS reported for gefitinib was considerably lower than the pooled OS from other publications due to the older and frailer patient population in the TULUNG Registry. Our observations of the TULUNG patient population frailty concur with this article.

The results of our analyses based on the data of 554 patients with common mutations and 24 patients with exon-20 insertions support the conclusions of Choi *et al.* based on

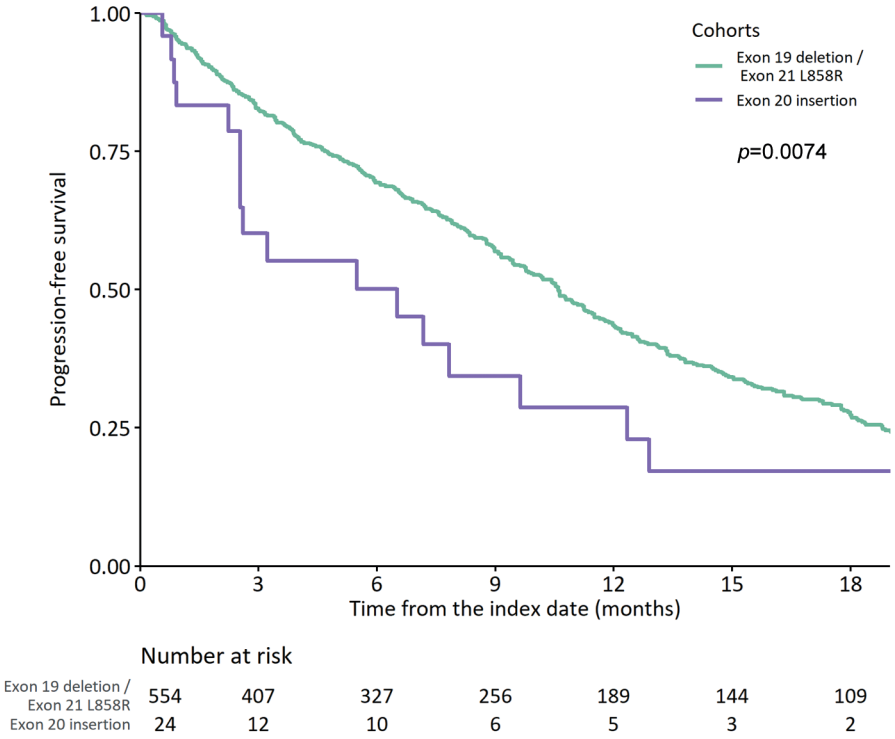

Figure 1. *Comparison of progression-free survival in the narrowed population. The graph shows the curves for the cohort with common EGFR mutations (green) and that with exon-20 insertion (purple) based on Kaplan–Meier estimates.*

Table VIII. *Estimates of PFS, OS, and TTNT from index date in narrowed population.*

	All (N=578)	Exon 20 insertions (N=24)	Common mutations (N=554)	*p*-Value
PFS[1] [months]				
Median (95%CI)	10.5 (9.4-11.3)	6.5 (2.5-12.9)	10.6 (9.6-11.5)	**0.007**
6-month PFS (95%CI)	0.685 (0.646-0.727)	0.502 (0.329-0.765)	0.693 (0.654-0.735)	
1-year PFS (95%CI)	0.429 (0.387-0.476)	0.287 (0.142-0.579)	0.436 (0.393-0.483)	
OS[1] [months]				
Median (95%CI)	23.6 (21.0-28.6)	18.0 (8.6-NA)	23.9 (21.3-29.0)	0.232
6-month OS (95%CI)	0.865 (0.836-0.895)	0.813 (0.662-0.998)	0.867 (0.838-0.898)	
1-year OS (95%CI)	0.742 (0.704-0.783)	0.625 (0.435-0.898)	0.747 (0.708-0.788)	
TTNT[2] [months]				
Median (95%CI)	43.0 (43.0-43.0)	12.9 (12.9-12.9)	44.4 (44.4-44.5)	0.176
6-month TTNT	0.878 (0.848-0.905)	0.763 (0.565-0.917)	0.883 (0.852-0.910)	
1-year TTNT	0.746 (0.706-0.785)	0.600 (0.389-0.818)	0.753 (0.712-0.792)	

[1]Values were obtained using Kaplan–Meier estimation. [2]Values for TTNT were computed as (1 - cumulative incidence). PFS: Progression-free survival; OS: overall survival; TTNT: time to next treatment. *p*-Value in bold indicates statistical significance.

the data of 53 patients, namely, that common mutations are associated with a more favorable PFS and OS (14).

Limitations. The TULUNG Registry does not include all NSCLC patients but exclusively those patients treated with high-value therapies. Hence, patients who have never received them are not represented. Since our index date is later than the diagnosis date, OS and PFS are biased downwards (shorter) compared to other studies. Patients who did not sign an informed consent to provide their medical

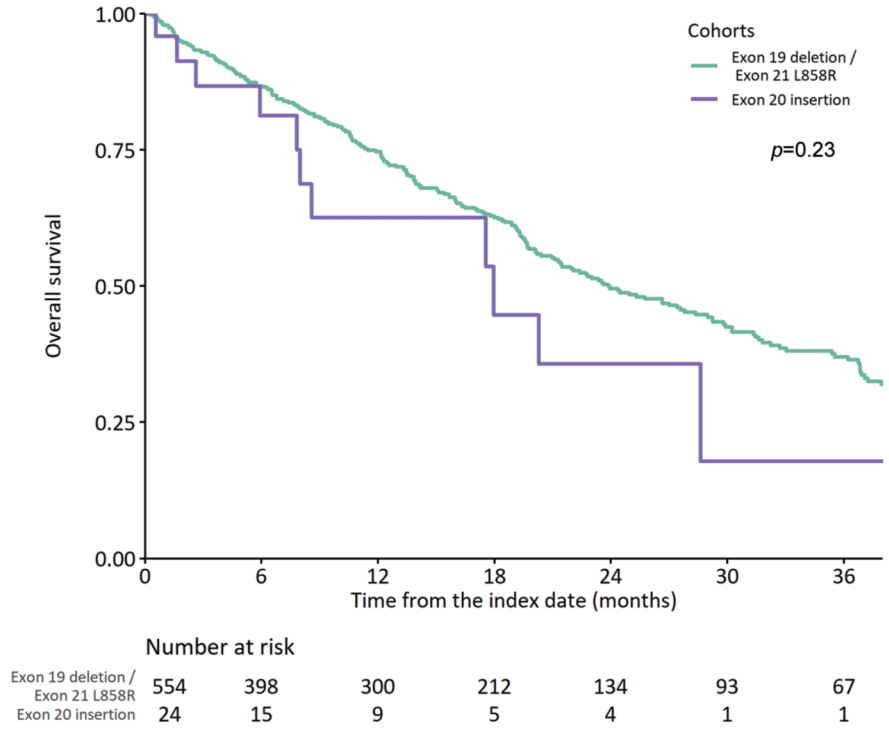

Figure 2. *Comparison of overall survival in the narrowed population. The graph shows the curves for the cohort with common EGFR mutations (green) and that with exon-20 insertion (purple) based on Kaplan–Meier estimates.*

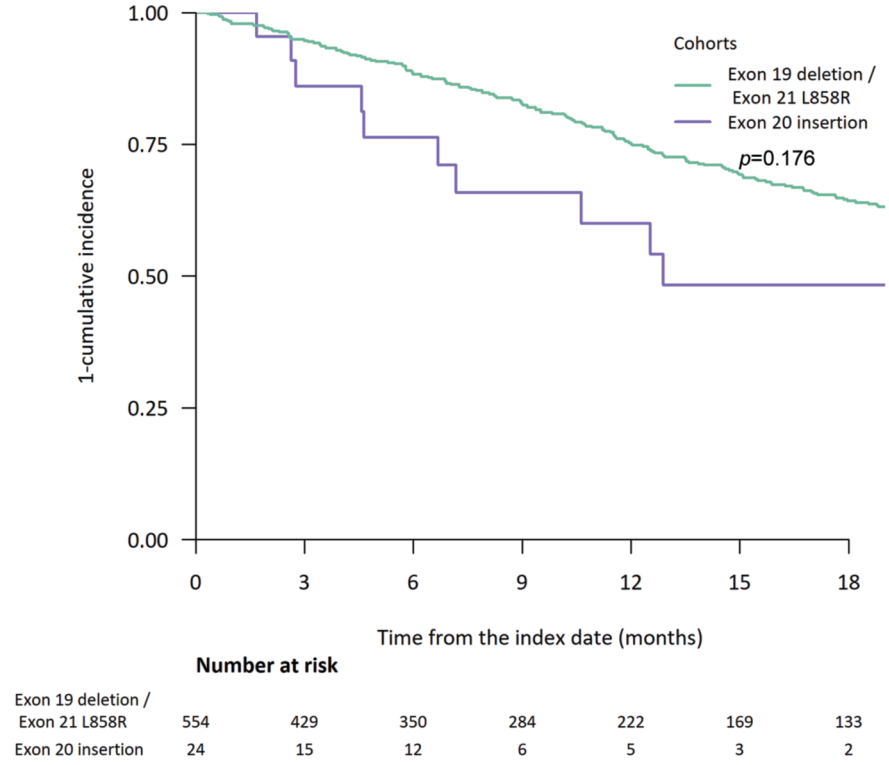

Figure 3. *Comparison of time to next treatment in the narrowed population. The graph shows the curves for the cohort with common EGFR mutations (green) and that with exon-20 insertion (purple) based on the cumulative incidence function.*

Table IX. *HR estimates in narrowed population.*

	HR (95%CI)	*p*-Value
Cox model for PFS	Group	
Common mutations	Ref. category	-
Exon-20 insertions	1.86 (1.17-2.95)	**0.009**
Cox model for OS	Group	
Common mutations	Ref. category	-
Exon-20 insertions	1.44 (0.79-2.64)	0.235
Fine-Gray model for TTNT	Group	
Common mutations	Ref. category	-
Exon-20 insertions	1.46 (0.72-2.95)	0.300

HR: Hazard ratio; PFS: progression-free survival; OS: overall survival; TTNT: time to next treatment. *p*-Value in bold indicates statistical significance.

data are not included in the TULUNG Registry. Errors in abstraction, data entry errors, and missing data might have led to misnumbering and misclassification of therapy lines and to misclassification of patients on other characteristics, including the biomarker status.

Conclusion

In conclusion, there is a significant unmet clinical need in NSCLC patients with exon-20 insertion and new therapies are needed to improve survival and time to progression in these patients.

Conflicts of Interest

P Mahadevia and P Kunovszki are employees of Janssen and may own stock or stock options. K Sandstrom was formerly an employee of Janssen and may own stock or stock options. M Barinova and K Hurdalkova are employees of Institute of Biostatistics and Analyses Ltd., an organization which was contracted and paid by Janssen for data acquisition and analysis. M Bratova reports honoraria from Astra Zeneca, Roche and BMS. J Skrickova, M Pesek, P Opalka, L Koubkova, M Zemanova, M Hrnciarik, J Blazek, M Svaton, J Krejci, H Coupkova, D Dolezal, T Tuzova, L Holubec, O Fischer, M Cernovska report no conflicts of interest.

Authors' Contributions

Jana Skrickova, Milos Pesek, Petr Opalka, Leona Koubkova, Milada Zemanova, Michal Hrnciarik, Jiri Blazek, Martin Svaton, Jana Krejci, Helena Coupkova, Daniel Dolezal, Tana Tuzova, Lubos Holubec, Parthiv Mahadevia, Kristina Sandstrom: Research plan, Methods review, Literature search, Review of draft, Review of final publication. Peter Kunovszki: Research plan, Methods review, Project coordination, Publication plan, Draft writing, Review of draft, Review of final publication. Magda Barinova: Research plan, Methods review, Project coordination, Draft writing, Review of draft, Review of final publication. Karolina Hurdalkova: Research plan, Methods review, Data analysis, Draft writing, Review of draft, Review of final publication. Ondrej Fischer, Marketa Cernovska: Research plan, Methods review, Review of draft, Review of final publication. Monika Bratova: Research plan, Methods review, Medical plan and review, Review of draft, Review of final publication.

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