Prevalence, real-world treatment patterns and survival outcomes of uncommon EGFR mutations in non-small cell lung cancer (NSCLC) patients in Canada

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Date: February 3, 2023

Location: Princess Margaret Cancer Centre, University Health Network (Toronto)

Abstract (Nederlands)

Introductie

Real-world bewijs rond *uncommon* epidermale groeifactor receptor (EGFR) mutaties in Canadese niet-kleincellig longkanker (*NSCLC*) patiënten is beperkt. Vanwege het geringe aantal patiënten met deze *uncommon* EGFR-mutaties zijn *single-arm* trials zeer gebruikelijk en is een *real-world* vergelijkingsarm noodzakelijk. Daarom is het doel van deze *real-world* analyse het opdoen van kennis over de prevalentie, klinisch-demografische gegevens, *real-world* behandelpatronen en overleving bij patiënten met deze *uncommon* EGFR-mutaties in Canada.

Methode

Er is een retrospectieve, observationele cohortstudie uitgevoerd onder patiënten met EGFR gemuteerde niet-kleincellig longkanker. Gegevens omtrent prevalentie, klninsch-demografische gegevens, behandelpatronen en klinische uitkomsten werden verzameld en deze werden vergeleken in patiënten met klassieke EGFR-mutaties tegenover drie subgroepen van *uncommon* EGFR-mutaties (complex, exon 20 inserties, overige *uncommon*).

Resultaten

Van de 669 EGFR-positieve patiënten had 79,5% een klassieke mutatie en 20,5% een *uncommon* mutatie. Complexe mutaties en exon 20 inserties zijn de meest voorkomende *uncommon* mutaties onder alle *uncommon* mutaties (respectievelijk 34,3% en 35,8%), waarbij exon 20 inserties vooral voorkomen bij Kaukasische patiënten. Patiënten in een gevorderd stadium met klassieke mutaties en overige *uncommon* mutaties lijken voornamelijk te worden behandeld met EGFR tyrosine kinase remmers (EGFR TKI's), terwijl patiënten met exon 20 inserties echt anders werden behandeld (voornamelijk met chemotherapie of in klinische trials). Exon 20 inserties deden het, vergeleken met klassieke mutaties, significant slechter qua overleving (mOS: 21,2 vs 32,2 maanden, mPFS: 5,8 vs 12,7 maanden).

Conclusie

Deze bevindingen onderstrepen de noodzaak van nieuwe behandelopties voor patiënten met EGFR exon 20 inserties en het identificeren van meer patiënten met *uncommon* EGFR mutaties. Daarom is voor het creëren van een *real-world* vergelijkingsarm het van belang om meer patiënten uit verschillende centra in Canada te includeren.

Abstract

Introduction

Real-world evidence around uncommon epidermal growth factor receptor (EGFR) mutations in Canadian non-small cell lung cancer (NSCLC) patients is limited. Due to a low number of patients with these uncommon EGFR mutations, single-arm trials are very common and a real-world comparison arm is necessary. Therefore, the overarching aim of this real-world analysis is to obtain knowledge of the prevalence, demographics, real-world treatment patterns and survival outcomes in patients with these uncommon EGFR mutations in Canada.

Methods

A single-centre, retrospective, observational cohort study was performed among patients with EGFR mutated NSCLC. Data on prevalence, demographics, treatment and clinical outcomes were collected and compared between patients with common EGFR mutations and three subgroups of uncommon EGFR mutations (complex, exon 20 insertions, other uncommon).

Results

Of 669 EGFR-positive patients, 79.5% had an EGFR common mutation and 20.5% had an EGFR uncommon mutation. EGFR complex mutations and EGFR exon 20 insertions are the most frequent uncommon mutation amongst all uncommon mutations (34.3% and 35.8%, respectively), with exon 20 insertions particularly prevalent amongst Caucasians. Advanced stage NSCLC patients with common mutations and other uncommon mutations appear to be treated mainly with EGFR tyrosine kinase inhibitors (EGFR TKIs), while patients with exon 20 insertions were treated really differently (mainly with chemotherapy or trial treatment). Exon 20 insertions, compared to common mutations, did significantly worse in terms of survival (mOS: 21.2 vs 32.2 months, mPFS: 5.8 vs 12.7 months).

Conclusion

These findings underline the need for new treatment options for patients with EGFR exon 20 insertions and the necessity to identify more patients harboring uncommon EGFR mutations to increase sample size. In order to create a real-world comparison arm, it is important to recruit more patient from different centres across Canada.

Introduction

There are two major types of lung cancer, non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). Though we have come to understand recently that the two types of lung cancer can transform into the other, especially in the case of targetable NSCLCs transforming into SCLCs after exposure to targeted agents. These two types of lung cancer are histologically, and often molecularly distinct, with different sensitivities to drug agents.[1] NSCLC is the most common form of lung cancer and accounts for 85-90% of all lung cancers in Canada. Often diagnosed in late stage, fewer than 17% of patients with NSCLC will live more than five years following diagnosis. Half of NSCLC cases are associated with known mutations.[2]

An estimated 15% of Canadians with NSCLC tumours have an activating mutation in the epidermal growth factor receptor (EGFR) gene in exons 18–21, the region encoding the tyrosine kinase domain. More frequent in lifetime never-smokers, the most common EGFR mutations are the exon 19 deletion (exon 19del) and the exon 21 L858 point mutation (L858R). Uncommon mutations, also found in exons 18–21, account for the remaining 8–18% of all EGFR mutations and might be more prevalent in men and smokers.[3-5] However, prevalence of these mutations may vary geographically and may even vary within Canadian regions.

Uncommon mutations can be classified through different manners, however have historically been categorized into three subgroups based on *in vitro* and *in vivo* response to EGFR tyrosine kinase inhibitors (TKIs):

- EGFR sensitizing mutations (G719X, S768I, L861Q, etc.)
- Exon 20 insertions
- De novo T790M mutations.[3]

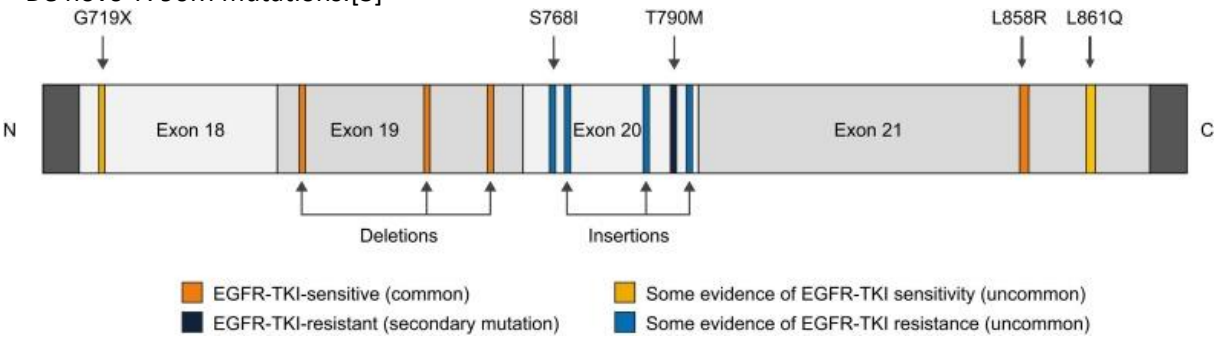


Figure 1. Overview of the different common and uncommon EGFR mutations, including sensitivity to EGFR tyrosine kinase inhibitors.

EGFR TKIs were introduced in Canada in 2010 for targeted treatment in EGFR-positive NSCLC patients, replacing chemotherapy in the first line for many EGFR-positive patients. Overall, response to EGFR-TKIs in patients with common mutations is better compared to patients with uncommon mutations.[5] Common exon 19del and exon 21 L858R mutations are considered sensitizing, because these mutations result in sensitizing the tumor to EGFR TKIs. These patients carrying the exon 19del or exon 21 L858R mutations are likely to have shrinkage of tumor and control of the cancer when administered with first-generation (erlotinib, gefitinib), second-generation (afatinib, dacomitinib), or third generation TKIs (osimertinib).[1,5] These drugs are generally effective as monotherapy at controlling the cancer (i.e., shrinking or keeping the cancer from growing) for periods of time, but eventually all patients will develop resistance to these agents. Generally the higher the generation TKI, the longer the median progression-free survival is. While the first generation agents have

median progression-free survivals of slightly under a year, osimertinib (third generation) has a median progression-free survival of 19 months.[6]

In contrast, whether available EGFR TKIs are effective in patients with uncommon EGFR mutations is currently unclear, as the response to treatment has been variable.[4] Firstly, patients harbouring an uncommon EGFR mutations are at least partially sensitizing, and can also be treated successfully (though temporarily) with first- and second-generation EGFR TKIs, as these sensitizing mutations might respond to these drugs. More specifically, patients carrying tumors with EGFR G719X, L861Q and S768I mutations have been reported to be associated with some response to second-generation EGFR TKIs.[7,8] However, another study reported poor response rate of S768I mutated patients to second-generation EGFR TKIs.[9] Secondly, de novo T790M mutations are known to be resistant to these first- and second-generation TKIs.[4] The third-generation TKI osimertinib is designed for tumours that have an acquired T790M resistance mutation. This T790M resistance mutation can originate after patients are treated with a first- or second-generation TKI for a common EGFR mutation. However, osimertinib was also found to be effective in patients with these common exon 19del and exon 21 L858R mutations. De novo T790M mutations can also be targeted by osimertinib, although clinical evidence is lacking and patients are treated empirically similarly to patients with an acquired T790M mutation.[10] Due to this promising broad spectrum, osimertinib is being assessed for other uncommon EGFR mutations in the Canadian-based trial OCELOT.[4,11] Lastly, patients harbouring EGFR exon 20 insertions have been especially difficult to treat. First- and second-generation EGFR TKIs are known to have a low response-rate in these patients.[12] Moreover, osimertinib has a low response rate in these patients and therefore the preferred treatment in patients with exon 20 insertions has been a platinum doublet or enrolment in a clinical trial.[4,12]

A new drug that specifically targets exon 20 insertions amivantamab was approved by Health Canada on April 4th 2022.[13,14] Other new potential drugs that target exon 20 insertions include mobocertinib (already approved by the FDA in the United States), sunvozertinib (phase I), poziotinib (phase II) , tarloxitinib (phase II) and CLN-081 (phase II).[15-17]

Once these new drugs are approved on the basis of safety and efficacy by Health Canada , cost-effectiveness is assessed by Canada's Drug and Technology Agency (CADTH) in order for the drugs to become publicly reimbursed in a process known as a health technology assessment (HTA).[18] If the drug is deemed potentially cost-effective by CADTH, the Patented Medicines Pricing Review Board (PMPRB) regulates the pricing ranges of drugs, which form the basis of each individual province's private negotiations with the pharmaceutical company.[19] A major part of HTA, is the comparison between efficacy, typically measured as overall survival (OS) or progression-free survival (PFS), of the new therapy with standard-of-care (SOC) therapies. In the case of the above new (potentially) approved drugs against uncommon EGFR mutations, a phase III randomized trial may be infeasible due to small numbers of patients and single-arm phase II trials are common. Single-arm trials do not include concurrent controls and therefore historical control data needs to be collected.[20] In other words for HTA to occur, a real-world comparison arm is needed. Even in the setting of a phase III trial, the SOC arm in the trial is expected to be compared with real-world data to document that the SOC arm has similar clinico-demographics and survival characteristics to real-world data.

Real-world data on prevalence, treatment patterns and survival outcomes in patients harboring uncommon EGFR mutations derived from Canadian sources, has thus become important to collect. Therefore, the overarching aim of this real-world analysis is to obtain knowledge of the prevalence, demographics, treatment patterns and survival outcomes in patients with these uncommon EGFR mutations in Canada. In this case, we utilized data from a single institution, Princess Margaret Cancer Centre, the largest free-standing cancer centre in Canada.

Methods

Study design and population

This analysis is a single-centre, retrospective observational cohort study, where EGFR-positive NSCLC patients were included (see below for specific inclusion criteria). This analysis was performed at the Princess Margaret Cancer Centre (PMCC), part of University Health Network (UHN) in Toronto, Canada. Data cut-off was Jan 11th 2023.

The inclusion criteria for the population used to estimate prevalence differed slightly from the population used for the treatment and survival analysis. For the prevalence part, specific selection criteria were formed to only include patients that were tested for both common and uncommon EGFR mutations, in order to prevent misclassification bias. For the treatment and survival analysis, a broader cohort of EGFR-positive patients was used, since including as many patients as possible was crucial in order to increase the sample size (*appendix 1*).

Specific criteria for assessment of prevalence

Inclusion Criteria:

- Patients ≥ 18 years at cancer diagnosis
- Patients were diagnosed with primary lung adenocarcinoma.
    - Patients diagnosed with this subtype of NSCLC are extensively tested for molecular alterations, because most molecular alterations in NSCLC occur in adenocarcinomas.
- Patients were diagnosed between January 1st 2015 and Dec 31st 2019.
    - Before January 1st 2015, most patients were only tested for exon 19 deletions and exon 21 L858R. After December 31st 2019, not all EGFR patients were entered into the database.
- Accessible/available molecular testing reports/documentation to confirm type(s) of both uncommon and common molecular alteration(s).
    - See *molecular platforms* for more details.

Exclusion Criteria:

- Patients only tested for common mutations by EGFR RFLP or other tests.
- Patients diagnosed before Jan 1st 2015 and after Dec 31st 2019.
- Patients with EGFR amplifications.

Additional included patients only in the survival analysis

- Patients with any other subtype of NSCLC.
- Patients confirmed to have an EGFR mutation by any testing platform.
- Patients diagnosed before Jan 1st 2015 or after December 31st 2019.

Identification of EGFR mutations

Definitions uncommon and common mutations

Common EGFR mutations were defined as exon 19 deletions or exon 21 L858R mutations. All other EGFR mutations were considered to be uncommon mutations. EGFR amplifications were not considered for this analysis (as the drugs target the mutations, not amplifications, gene expression,

or protein expression), unless the patient's tumor also had an actual EGFR mutation. Patients with both a common or uncommon mutation plus a T790M resistance (i.e. mutation acquired after being treated with an EGFR TKI) mutation were included with the primary mutation.

For assessment of prevalence (or proportion of EGFR subtypes), patients with only a T790M mutation in the absence of a second EGFR mutation, or patients with a T790M mutation without having been treated with EGFR TKI, were included as de novo T790M mutated patients. Patients with $\geq$ 1 mutation, of which one of the mutations was **not** T790M resistance mutation, were included as patients with complex mutations.

For the survival analysis, the main categories of patients that were identified were: ''*common mutations*'', ''*exon 20 insertions*'', ''*complex mutations*'' and ''*other uncommon mutations*''.

In assessing the treatment patterns, complex mutations were not considered standard part of the ''*other uncommon mutations*'' group, but were divided and put into one of the three categories according to treatment intention (*appendix 2)*. Therefore, patients with complex mutations were divided over the three EGFR mutation subgroups as followed:

- Patients with tumors carrying the EGFR exon 20 insertion mutation, regardless of the co-mutation, were placed in the ''*exon 20 insertions*'' group, as these patients were not frequently started on the typical EGFR TKIs. These exon 20 insertions were considered to be mostly resistant to common EGFR TKIs, such as gefitinib, erlotinib and osimertinib, even if they also had other common or uncommon mutations.
- Patients with a combination of an uncommon (non-exon 20 insertion) and a common mutation were included in the ''*common mutations*'' group, as these patients are mostly treated according to their primary common mutation (and mostly had response to therapy).
- Patients with >1 common mutation in the absence of any uncommon mutations were included in the ''*common mutations*'' group, as these patients had tumors that were generally responsive to standard EGFR TKIs.
- Patients with >1 uncommon (non-exon 20 insertion) mutations in the absence of any common mutations were included in the ''*other uncommon mutations*'' group.

Molecular platforms

In estimating the prevalence of various EGFR mutations within the population, we only included patients who had tumors that were tested using molecular platforms that tested for both common and uncommon mutations in EGFR exon 18-21, in order to prevent misclassification bias. The molecular testing platforms used in this analysis were:

- Extensive next generation sequencing (NGS): Guardant360, Foundation Medicine Assay, Oncomine Comprehensive Assay v3, FoundationOne assays.
- Limited NGS: TruSight® Tumor 15 (NGS:TST15).
- EntroGen® EGFR Mutation Analysis Kit for Real-Time PCR (EGFR-RT52).

Excluded were those platforms that only tested for specific resistance mutations or only for common mutations:

- EGFR restriction fragment length polymorphism (EGFR-RFLP), which only tested for common mutations but not the uncommon mutations (mainly prior to 2015).
- Droplet digital polymerase chain reaction (ddPCR), which tested for T790M resistance mutations (with or without common EGFR mutations, but not the uncommon mutations).

Clinical data

Clinical data was derived from radiology reports, clinical notes, pathological or cytological reports and radiation treatment reports. Prior to June 4, 2022 this clinical data was abstracted from the Quadramed Electronic Patient Record (EPR). After June 4, 2022 this clinical data was abstracted from the health information system Epic, because Princess Margaret Cancer Centre started using Epic from this date onwards. TNM stage was physician-assessed according to the eighth International Association for the Study of Lung cancer (IASLC) Staging Project.[21] Eastern Cooperative Oncology Group performance status (ECOG PS) at diagnosis and response rate were physician-assessed.

Information on drugs delivered and administered by the pharmacy at UHN was derived from the Oncology Patient Information System (OPIS). This information included both chemotherapy administration and oral targeted therapy distribution to patients. Clinical data was subsequently entered into ACORN, which is a database that holds information on NSCLC patient demographics, radiation treatment, metastases, surgeries and systemic treatment. Through this database, the statistical analysis was performed.

The University Health Network Research Ethics Board has reviewed and approved the Renewal (REB 06-0639) for CARMA-BROS (UHN is one of the CARMA-BROS sites) and therefore this analysis.[22]

Study outcomes

The primary objectives of this study included estimation of the prevalence of common and uncommon EGFR mutations, determining differences in clinico-demographics between common and uncommon mutations, evaluation of treatment patterns across different lines of treatment and assessment of overall survival (OS), disease-free survival (DFS) and progression-free survival (PFS).

Statistical methods

Estimation of the prevalence of uncommon EGFR mutations amongst patients who have EGFR mutations in total was reported descriptively as a proportion and visualized in a pie chart. The specific types of uncommon and complex mutations were described as bar graphs in the same figure. Moreover, yearly prevalence was assessed to check for bias due to a change of molecular platforms over the years. Clinico-demographic variables were compared using chi-squared test or Fisher's exact test where appropriate for categorical variables and Kruskal-Wallis tests for continuous variables.

Sankey flow diagrams were constructed to display the distribution of the first, second and third line of treatment per EGFR mutation subgroup. Categories of treatment included were chemotherapy, immunotherapy, chemotherapy with immunotherapy, EGFR TKIs and trial treatment.

Early stage patients were defined as patients treated with curative intent (mostly stage I-IIIA) and advanced stage patients were defined as patients treated with palliative intent (mostly stage IIIB-IV). OS in the early-stage population was defined as the time from date of initial diagnosis to death or date of last follow-up. OS was defined as the time from date of advanced stage diagnosis to death or date of last follow-up in the advance stage population. PFS was defined as time from start of first line of treatment to first date of progression, date of death, or date of last follow-up, whichever was the earliest. Recurrence-free survival (DFS) was defined as time from date of initial diagnosis to first date of progression/recurrence, date of death, or date of last follow-up, whichever was the earliest. Kaplan-Meier curves for both OS and PFS were stratified by EGFR mutation type and treatment type, and compared using log-rank tests. Multivariable Cox proportional hazards model were performed adjusting for stage at diagnosis for early stage patients. RStudio version 1.4.1106 was used for statistical analysis.[23]

Results

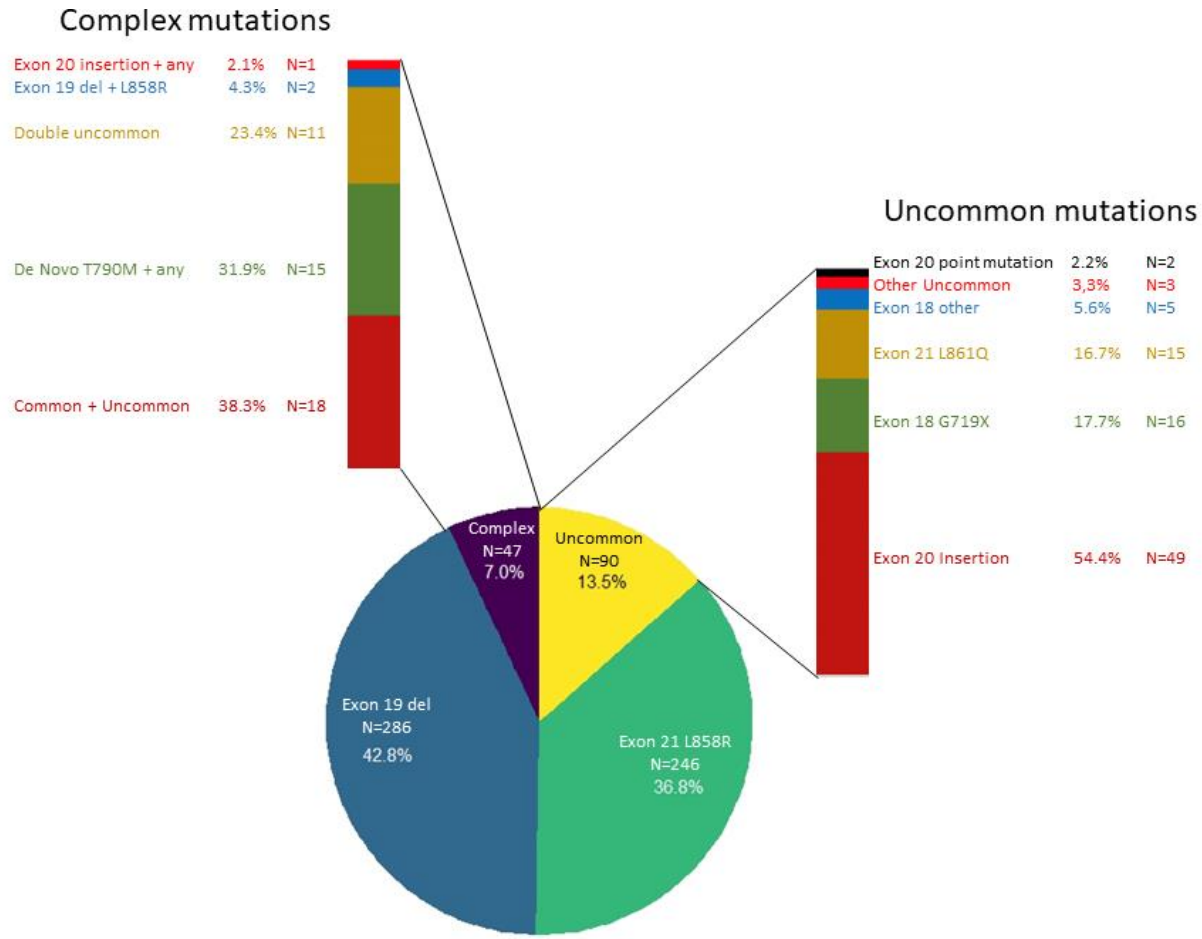
Prevalence (or proportion) of different subtypes of EGFR mutations

Amongst 2253 NSCLC patients with the adenocarcinoma subtype diagnosed between 2015-2019, 669 patients (29.7%**)** tested positive for an EGFR mutation. Of 669 EGFR-positive NSCLC patients, 79.5% harbored a single common mutation, 13.5% had a single uncommon mutation and 7.0% contained complex mutations (*figure 2)*. Exon 19 deletions (42.8% of all EGFR mutations) were slightly more prevalent in these patients than exon 21 L858R mutations (36.8% of all EGFR mutations).

Of the 137 patients (20.5% of total EGFR mutations) that harbored either a single uncommon mutation or a complex mutation, 90 patients (65.7%) had a single uncommon mutation while 47 patients (34.3%) a complex mutation. Exon 20 insertions were the most prevalent single uncommon mutation amongst single uncommon mutations (54.4%), followed by exon 18 G719X point mutation (17.7%) and exon 21 L861Q point mutation (16.7%; *figure 2)*.

Forty-seven patients harbored a complex mutation, which were categorized into five different types of combinations (*figure 2)*. The most frequent combination was a common mutation plus an uncommon mutation, being responsible for 38.3% of complex mutations. Second, de novo T790M point mutations (31.9%) were always present as a complex mutation, mostly with a concomitant exon 19 deletion or exon 21 L858R mutation. Only in one case did a de novo T790M point mutation occur with an uncommon mutation (exon 20 mutation plus a Cys797Gly point mutation). Third, complex mutations consisting of two uncommon mutations occurred in 23.4%. Notably, a frequent combination of two uncommon mutations was exon 18 G719X and exon 20 S768I point mutations (6 patients; 12.8% of complex mutations). Fourth, in only two patients (4.3%) was a combination of the two common mutations observed. Finally, complex mutations involving exon 20 insertions only occurred in only one patient (2.1%). Yearly prevalence of the different types of mutations was similar *(appendix 4-5*, p=0.149).

Figure 2. Frequency of EGFR mutations amongst 669 EGFR-positive adenocarcinoma patients diagnosed between Jan 1st 2015 and December 31st 2019. Mutations are categorized as exon 19 deletion, exon 21 L858R, uncommon mutation or complex mutation. Uncommon and complex mutations are further categorized in the specific sub-mutations.



Clinico-demographic variables

Patient characteristics of 669 EGFR-positive patients, divided by mutation type, are shown in *table 1.* The proportion of patients who were Asian was significantly lower among those with uncommon mutations than among patients with common mutations (37.7% vs 65.0%, p=0.001). Subgroup analysis of specific uncommon mutations showed that EGFR exon 20 insertions were the main reason for this lower proportion, as only 29.7% of patients with exon 20 insertions occurred in Asians, when compared to 50-71% for the other EGFR mutation subtypes (*appendix 6)*. Exon 20 insertions seemed to be particularly prevalent in Caucasians, as 62.2% of total exon 20 insertions occurred in Caucasians.

The proportion of never smokers was significantly lower among patients with uncommon mutations than that among patients with common mutations (47.2% vs 71.6%, p<0.001). The same subgroup analysis (*appendix 6)* demonstrated that other (non-exon 20 insertion) uncommon mutations were mainly driving this lower prevalence of uncommon mutations in never smokers, as only 32.5% of other uncommon mutations occurred in never smokers.

Amongst 47 patients with complex mutations, patients were more likely to be Asian (60.5%) and never smokers (55.3%), rendering these patients to be more similar to the common mutations than the exon 20 or uncommon mutation categories. Initial stage at diagnosis differed significantly between the groups (p=0.040), where the uncommon mutations were slightly more likely to have been diagnosed at an earlier stage (Stage I-III) than the other EGFR subtypes. No differences in age, sex, year of diagnosis or ECOG performance status at initial diagnosis between the subgroups were observed.

Characteristic	Category	Common	Complex	Uncommon	Total	p-value
Total N (%)		N = 532 (79.5)	N = 47 (7.0)	N = 90 (13.5)	N = 669	
Age at Diagnosis (in years)	Median (IQR)	67.4 (57.8-75.1)	66.1 (59.3-74.9)	66.3 (59.4-76.1)	67.0 (58.0-75.2)	0.966
Sex	Female	362 (68.0)	30 (63.8)	65 (72.2)	457 (68.3)	0.580
	Male	170 (32.0)	17 (36.2)	25 (27.8)	212 (31.7)	
Ethnicity	Asian	266 (65.0)	23 (60.5)	23 (37.7)	312 (61.4)	0.001
	Caucasian	109 (26.7)	12 (31.6)	33 (54.1)	154 (30.3)	
	Other	34 (8.3)	3 (7.9)	5 (8.2)	42 (8.3)	
	Missing	123	9	29	161	
Smoking status	Current smoker	19 (3.7)	3 (6.4)	11 (12.4)	33 (5.1)	<0.001
	Ex-smoker	127 (24.7)	18 (38.3)	36 (40.4)	181 (27.8)	
	Never smoker	368 (71.6)	26 (55.3)	42 (47.2)	436 (67.1)	
	Missing	18	0	1	19	
Packyears	Median (IQR)	20.0 (10.0 to 30.0)	13.0 (5.0 to 32.0)	17.5 (10.0 to 30.0)	20.0 (10.0 to 30.0)	0.832
Stage at diagnosis	I	184 (34.6)	12 (25.5)	24 (26.7)	220 (32.9)	0.040
	II	21 (3.9)	4 (8.5)	7 (7.8)	32 (4.8)	
	IIIA	37 (7.0)	4 (8.5)	15 (16.7)	56 (8.4)	
	IIIB	13 (2.4)	2 (4.3)	5 (5.6)	20 (3.0)	
	IV	276 (51.9)	25 (53.2)	39 (43.3)	340 (50.8)	
	Missing	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)	
Diagnosis year	2015	103 (19.4)	9 (19.1)	14 (15.6)	126 (18.8)	0.406
	2016	132 (24.8)	8 (17.0)	18 (20.0)	158 (23.6)	
	2017	87 (16.4)	8 (17.0)	16 (17.8)	111 (16.6)	
	2018	116 (21.8)	17 (36.2)	25 (27.8)	158 (23.6)	
	2019	94 (17.7)	5 (10.6)	17 (18.9)	116 (17.3)	
ECOG at initial diagnosis	0	53 (10.0)	7 (14.9)	13 (14.4)	73 (10.9)	0.608
	1	102 (19.2)	10 (21.3)	20 (22.2)	132 (19.7)	
	>=2	20 (3.8)	3 (6.4)	3 (3.3)	26 (3.9)	
	Missing	357 (67.1)	27 (57.4)	54 (60.0)	438 (65.5)	

Table 1. Demographics and clinical characteristics of all EGFR-positive adenocarcinoma patients diagnosed between 2015-2019, stratified by common, uncommon, or complex mutation.

Treatment and survival analysis

By including patients of all NSCLC subtypes and years of diagnosis, an additional 58 patients were identified. Total patients included for this part of the analysis was therefore 727 patients. The NSCLC subtype adenocarcinoma was still the most common, 95.2% (692 patients), of all EGFR-positive cases (*appendix* 7). 315 patients (43.3%) were diagnosed with curable NSCLC and 412 patients (56.7%) were diagnosed at incurable, palliative stages or moved at some point from the curative stage to the palliative stage (*appendix* 7). Of 73 patients tested positive for an exon 20 insertion, the S768_D770dup was the most frequent insertion that occurred (15.1%), followed by A767_V769dup (6.8%) and H773_V774dup (4.1%). Further, 30 patients (41.1%) were near-loop (A767-P772) mutants, 12 patients (16.4%) far-loop (H773-C775) mutants and two patients (2.7%) helical (E762-M766) mutants. In 37.0% of patients the specific insertion was undetermined or not reported (*appendix 3)*.

Treatment patterns

Amongst all EGFR-positive patients diagnosed with curative (early stage) disease, patients with exon 20 insertions or other uncommon mutation were more likely to receive curative systemic therapy compared to patients with common mutations (57.6% and 44.7% vs 32.4%, p=0.010; *appendix 8*). In all three groups this curative systemic therapy consisted of adjuvant chemotherapy (after surgical resection) for Stages IB-IIIA or a combination of chemotherapy-radiotherapy followed by immunotherapy for unresectable stage III. Type of surgery was in almost all cases a lobectomy or a wedge resection (*appendix* 8).

Amongst all patients diagnosed with incurable (advanced stage) disease (i.e. who had palliative treatment), patients harboring an exon 20 insertion or other uncommon mutation were less likely to receive first line of systemic treatment compared to patients with a common mutation (89.1% and 88.1% vs 98.0%, p<0.001; *appendix 9*). First line of treatment was similar in patients with common mutations and other uncommon mutations, where amongst all patients started on first-line of treatment, an EGFR TKIs was initiated in 87.2% and 82.9% of patients, respectively. In both of these groups gefitinib was the most extensive used drug. In common and other uncommon mutations, chemotherapy played an increasingly more important role in the second and third lines, whereas the role of trial treatment remained small (*figure 3AB)*.

In contrast, in patients with an exon 20 insertion that started on first-line of treatment, most were treated with chemotherapy (34.1%), trial treatment (31.7%) or an EGFR TKI (19.5%). Most used chemotherapeutic agent was pemetrexed/platinum doublet followed by pemetrexed maintenance (8 patients) and most used trial treatment was poziotinib (8 patients). Of all eight patients started on a first-line EGFR TKI, seven (17.1% of total first-line treatment started) were started on afatinib (*appendix 10)*. Compared to the first-line of treatment in exon 20 insertion patients, a similar ratio of trial treatment and chemotherapy was seen in both the second and third line (*figure 3C)*.

Reasons for stopping (*appendix 11)* amongst all patients that stopped first-line of treatment at any point were similar across all EGFR subgroups, with most frequent reasons being due to progression (54.5-75.6%) or due to toxicity (9.8-12.1%). Of 45 patients that stopped first-line of treatment due to toxicity, 18 patients (40.0%) were on an EGFR TKI (*appendix 12)*. In these 18 patients that were on a first-line EGFR TKI, skin toxicity (44.4%) was the most common reason for discontinuing the drug. Second most common stop reason due to toxicity in patients treated with an EGFR TKI was drug-induced pneumonitis (27.8%) and occurred in 4 out of 5 cases in patients on osimertinib. Third was hepatotoxicity (16.7%) and happened while all of these patients were on gefitinib.

Figure 3ABC. Sankey flow diagrams. Common mutations (A), other uncommon mutations (B) and exon 20 insertions (C). Dark blue line on the left presented full cohort. Each color represents a specific treatment type. Patients moved through lines of treatment, from left to right. Grey lines demonstrated the proportion of patients that moved from one specific line to another.

Figure 3A. Sankey flow diagram describing the flow of patients through the first three lines of treatment in patients with common mutations.

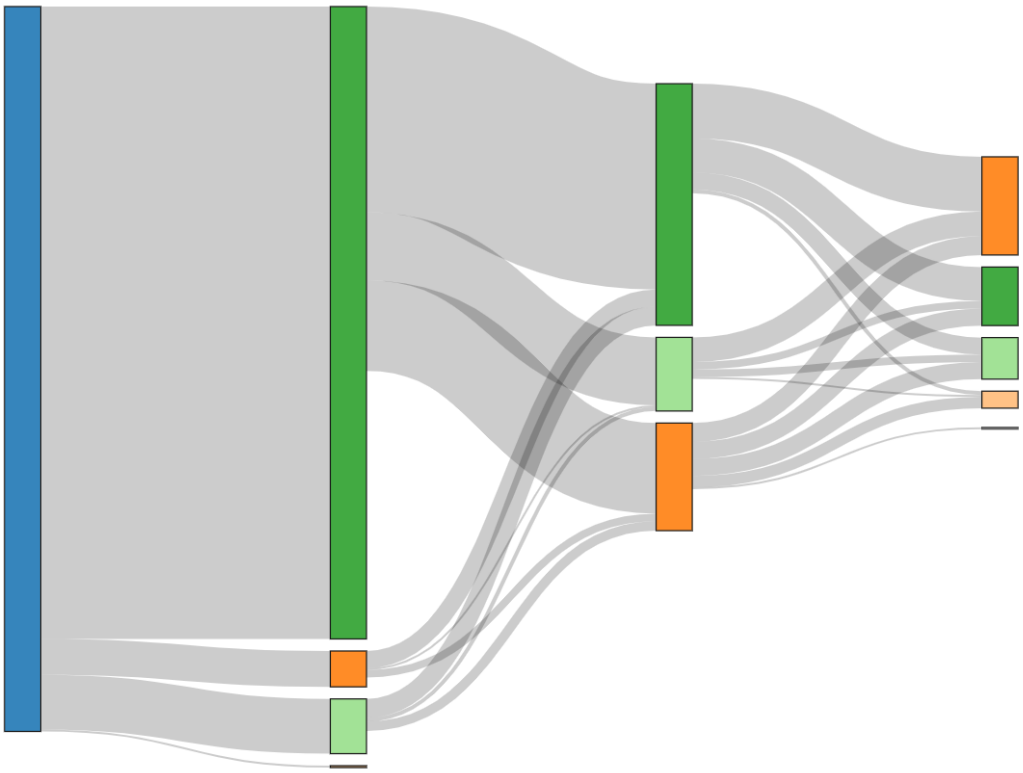


Figure 3B. Sankey flow diagram describing the flow of patients through the first three lines of treatment in patients with other uncommon mutations.

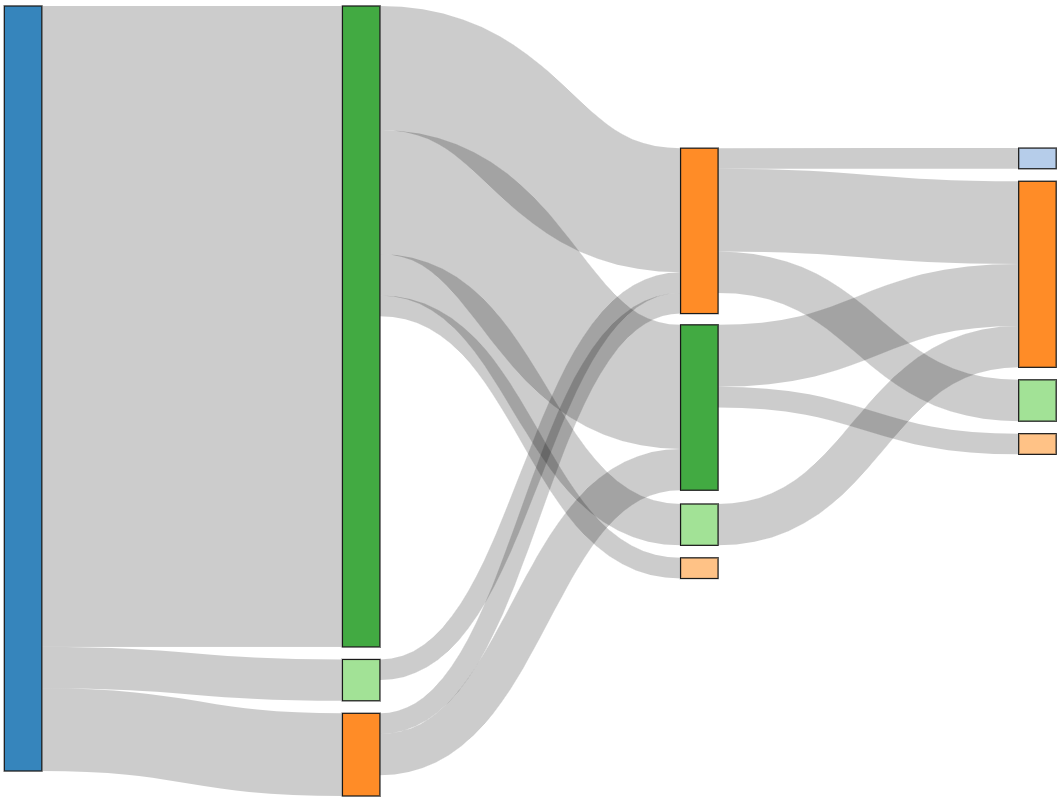
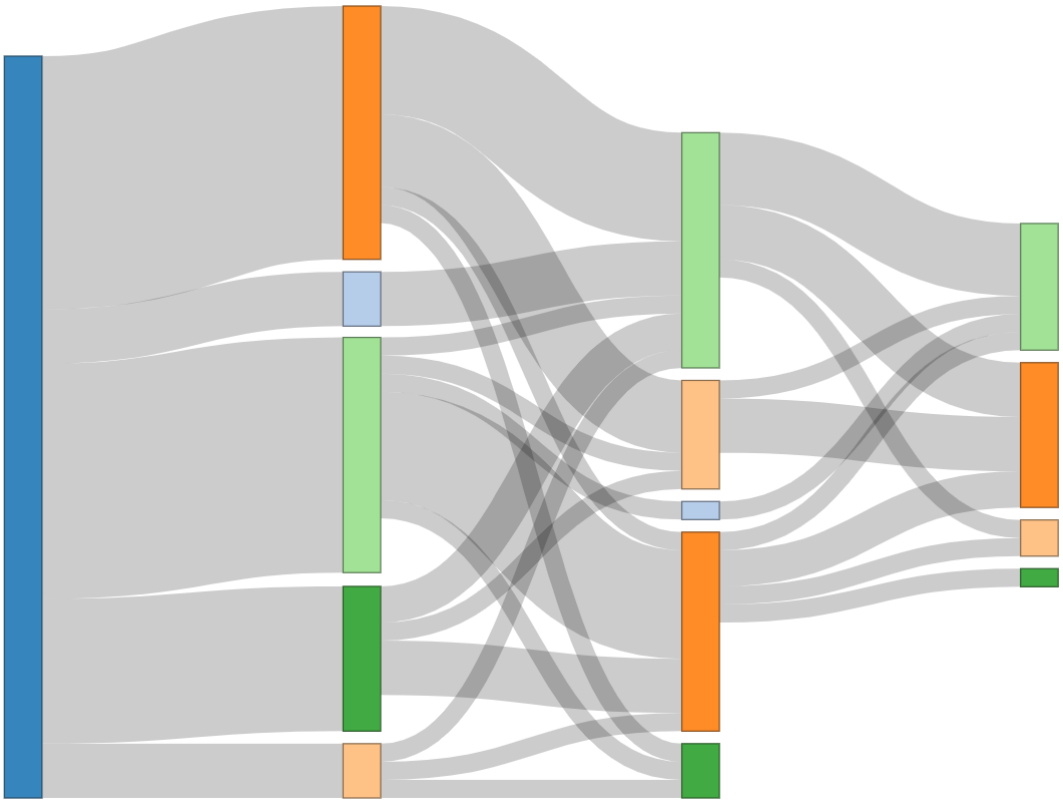


Figure 3C. Sankey flow diagram describing the flow of patients through the first three lines of treatment in patients with exon 20 insertions.



Overall survival

Median follow-up was 46.4 months for patients with common mutations, 49.9 months for patients with complex mutations, 54.7 months for patients with an exon 20 insertion and 60.0 months for patients with other uncommon mutations (*figure 4)*. Stratified by type of EGFR mutation, median OS in early stage NSCLC patients was not reached in any of the four groups (p=0.17). Probability of survival for patients with exon 20 insertions compared to common mutations, after performing a Cox proportional hazard adjusting for disease stage at diagnosis, was no longer significant (*appendix 13;* HR = 1.55, 95% CI: 0.76-3.19, p=0.232).

In advanced stage NSCLC patients, median OS was 21.2 (95% CI: 13.3-30.8), 26.0 (95% CI: 20.0-49.4), 30.0 (95% CI: 20.9-44.6) and 32.2 (95% CI: 27.8-35.7) months for exon 20 insertions, other uncommon mutations, complex mutations and common mutations, respectively (*figure 5)*. Probability of survival was significantly lower (i.e. a higher probability of expiring) for exon 20 insertion compared to common mutations (HR = 1.62, 95% CI 1.14-2.29, p=0.006). This was not the case for other uncommon mutations or complex mutations compared to common mutations.

Figure 4. Overall survival in early-stage EGFR-positive NSCLC patients starting from the date of early stage diagnosis. Stratified by EGFR mutation: common, complex, other uncommon or exon 20 insertion.

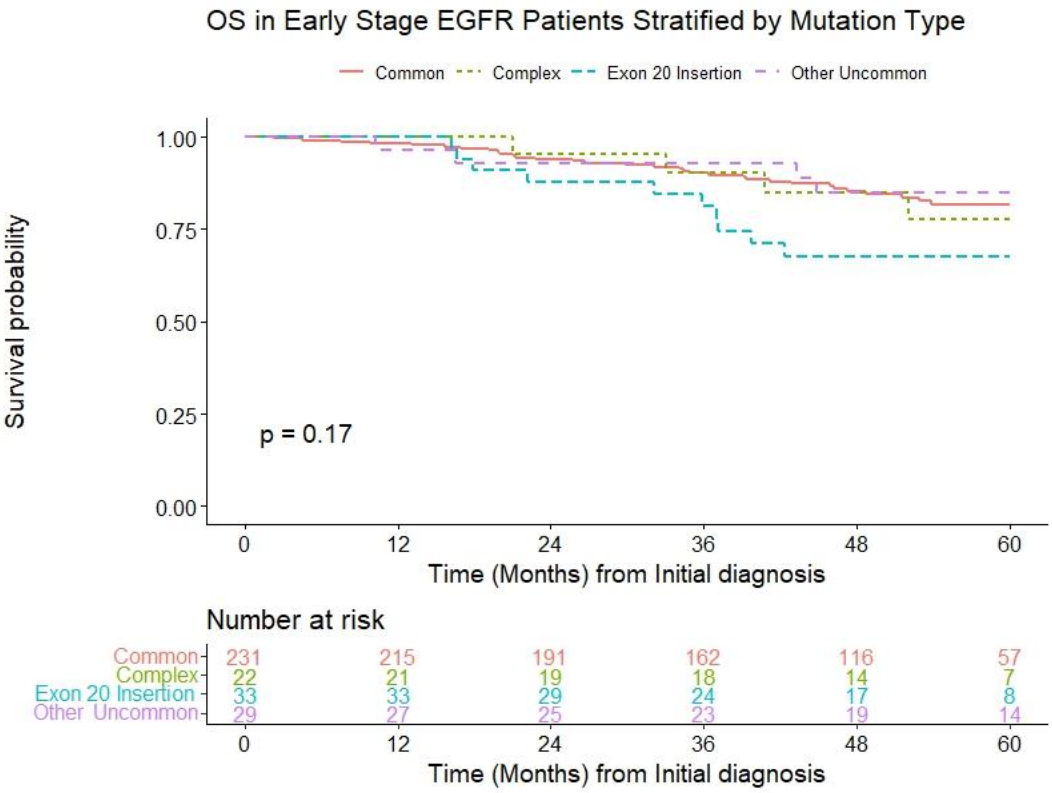
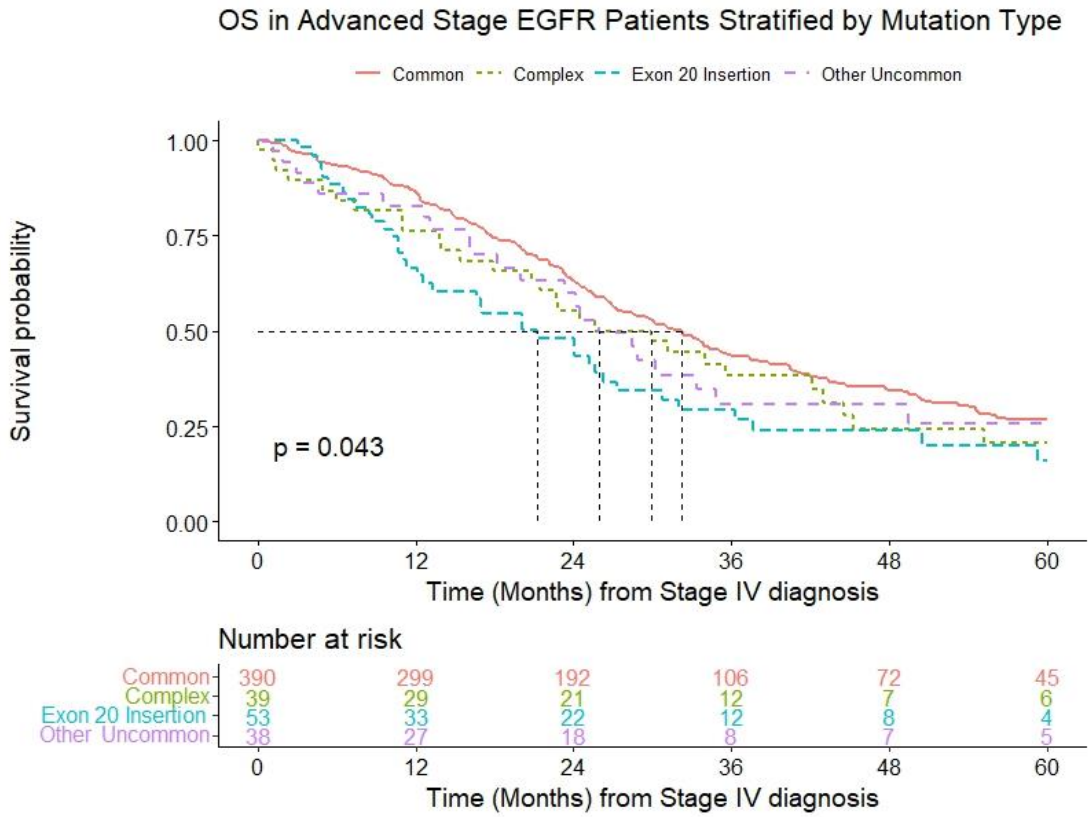


Figure 5. Overall survival in advanced stage EGFR-positive NSCLC patients starting from the date of advanced stage diagnosis. Stratified by EGFR mutation: common, complex, other uncommon or exon 20 insertion. Patients that were initially early stage NSCLC were included from the date of advanced stage diagnosis.



Disease-free survival and progression-free survival

Median disease-free survival (DFS) in early-stage patients was not reached for all EGFR mutation types (*figure 6 and appendix 13;* p=0.076*)*. Similar to OS in early stage patients, after adjusting for stage no significant difference in survival was observed between exon 20 insertions and common mutations (*appendix 13;* HR = 1.14, 95% CI: 0.68-1.91, p=0.626)

Median PFS was 5.8 (95% CI: 5.2-9.3), 10.4 (95% CI: 5.5-22.9), 12.5 (95% CI: 8.8-23.0) and 12.7 (95% CI: 11.6-14.2) months for exon 20 insertions, other uncommon mutations, complex mutations and common mutations, respectively (*figure 7A)*. PFS was significantly lower in patients harboring an exon 20 insertion compared to common mutations (HR = 1.99, 95% CI: 1.42-2.78, p<0.001). This difference was not observed between other uncommon mutations or complex mutations vs common mutations. Median PFS was 12.0 (95% CI: 11.4-13.5) and 15.9 (95% CI: 12.6-24.1) months for patients started on a first- or second generation TKI versus first-line osimertinib, respectively (*figure 7B)*. Median PFS for patients receiving first-line of treatment other than an EGFR TKI was 11.0 (95% CI: 6.9-19.1). Only 35 patients of 356 common mutated patients that started first-line treatment were not started on an EGFR TKI.

Figure 6. Disease-free survival in early-stage EGFR-positive NSCLC patients starting from the date of early stage diagnosis. Stratified by EGFR mutation: common, complex, other uncommon or exon 20 insertion.

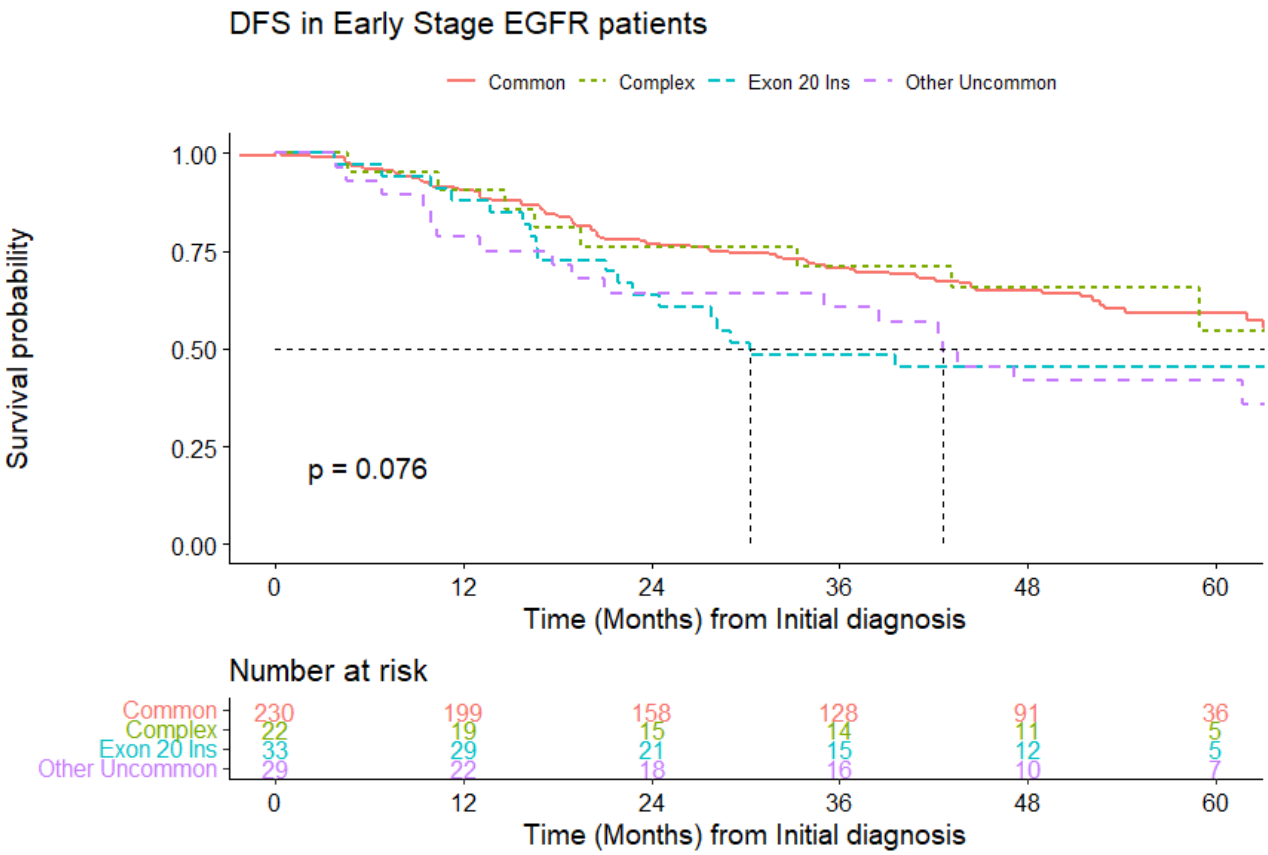
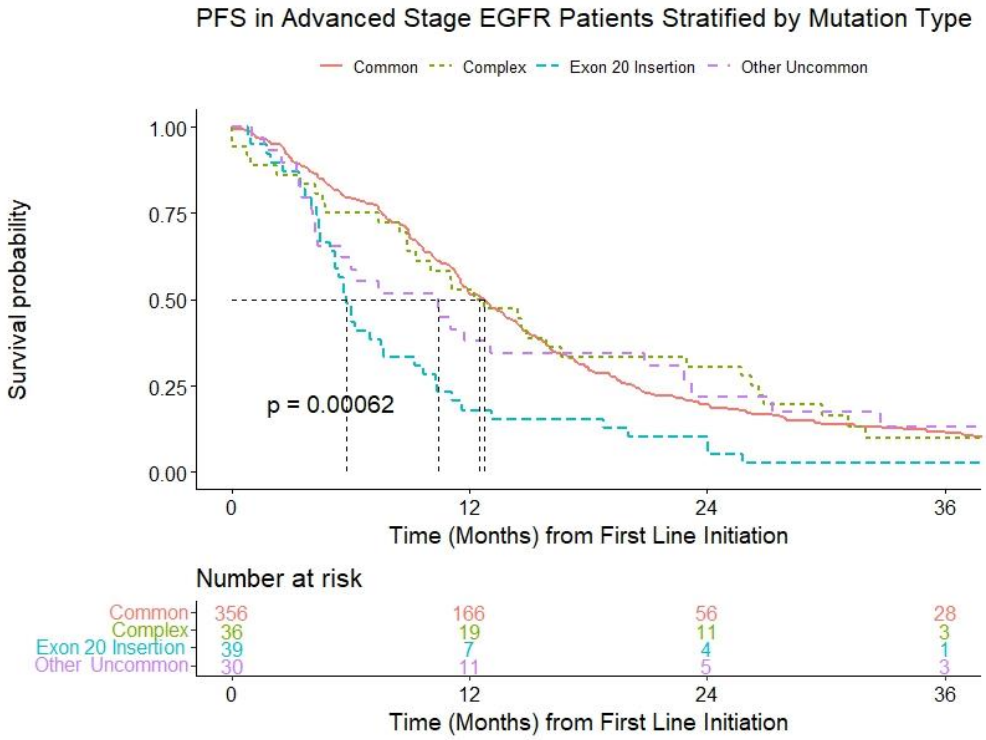
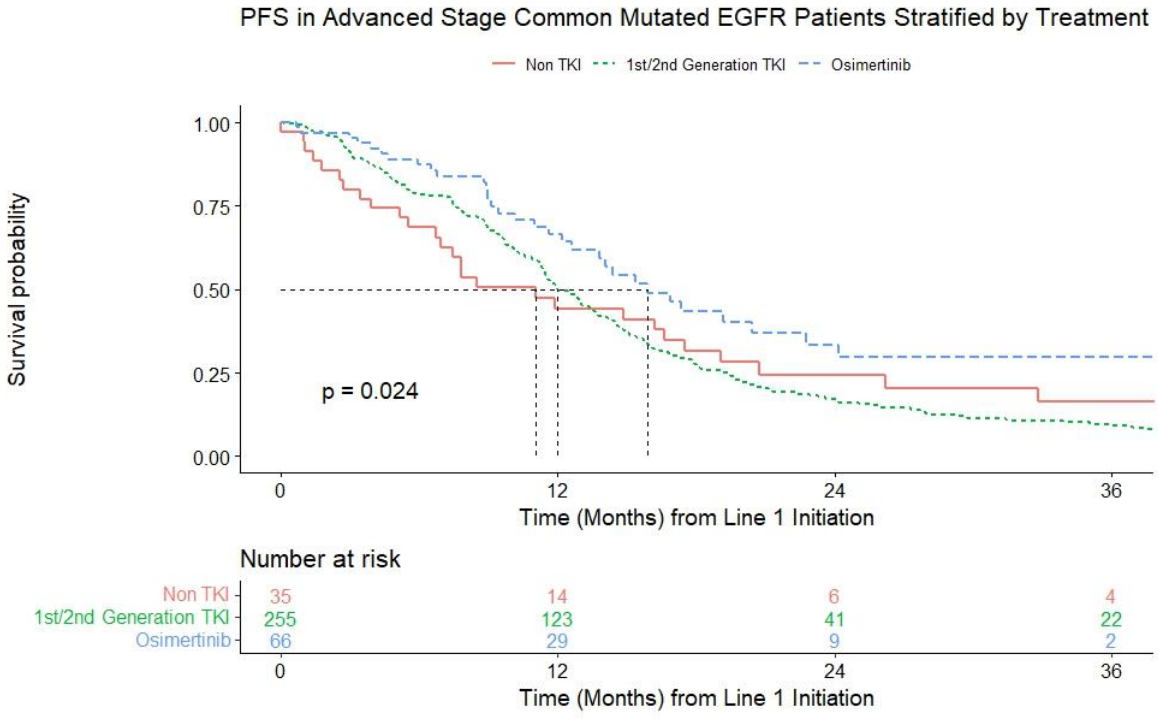


Figure 7AB. Progression-free survival in advanced stage EGFR-positive NSCLC patients starting from the initiation of first-line treatment. Stratified by EGFR mutation: common, complex, other uncommon or exon 20 insertion (6A). Progression-free survival in advanced stage NSCLC patients with a common mutation starting from the initiation of first-line treatment. Stratified by first-line osimertinib, first- or second generation TKI or non-TKI treatment (6B).

A



B



Discussion

This retrospective, real-world cohort study contributed to insights in prevalence, demographics, treatment patterns and survival outcomes of uncommon EGFR mutations in both early and advanced stage EGFR-mutated NSCLC patients in Canada. Exon 20 insertions and complex mutations were the most prevalent amongst all uncommon mutations. Exon 20 insertions were mainly treated with platinum-based chemotherapy or trial treatment in the first line, whereas common and other uncommon mutations were mainly treated with EGFR TKIs. It was demonstrated that advanced stage patients harboring exon 20 insertions did significantly worse in terms of survival (both OS and first-line PFS) when compared to patients with common, complex and uncommon mutations.

This analysis found that 79.5% of 669 EGFR-positive patients harbored a single common mutation and 20.5% a single uncommon or complex mutation. In a recent Canadian analysis involving patients with resected, early-stage NSCLC were tested for EGFR status, a very similar prevalence of EGFR mutations was found: 75.6% of EGFR mutations was a common mutation and 19.2% of total EGFR mutations was an uncommon or complex mutation.[24] Another recent Canadian analysis found that 84.3% of total EGFR-positive NSCLC patients had a common mutation, 3.1% a complex mutation and 12.6% an uncommon mutation. Our results are confirmatory.[25] In the screening for the ADAURA trial (a phase III RCT assessing efficacy and safety of osimertinib vs placebo in Canadian stage IB-IIIA NSCLC patients, following complete tumour resection), EGFR prevalence was assessed.[26] In this analysis a higher frequency of common mutations was found: 53% and 42% of all EGFR positive patients were exon 19 deletion or exon 21 L858R mutation positive, respectively. Only 10% of EGFR-positive patients harbored any uncommon mutation. A potential explanation for this is that complex mutations were not taken into account as such, though were counted as separate mutations. Finally, earlier published reviews assessing current literature on the prevalence of uncommon EGFR mutations reported slightly lower, but fairly similar frequencies of uncommon mutations amongst EGFR mutated NSCLC patients (10-18% and 8-18%).[27,28] The slightly higher proportion of uncommon mutations found in this analysis can be attributed to more extensive molecular testing for uncommon mutations in recent years. More specifically on the prevalence of exon 20 insertions, this study found that 7.5% of total EGFR-mutated patients had an exon 20 insertion. This is consistent with the proportions found in the above mentioned Canadian studies and a study from the USA (4.0-9.0%).[24,25,29]

Common mutations were found to be more prevalent in Asians and never smokers, whereas uncommon mutations were found to be more prevalent in Caucasians and smokers. This is in alignment with previous reported literature.[24,28,30,31] Exon 20 insertions compared to other uncommon mutations were found to be especially prevalent in Caucasians, which to our understanding has not been previously reported in literature. The recent suggestion of Ko et al that smoking contributes to the development of complex mutations, was not observed in this analysis.[30]

For early stage NSCLC patients harboring an exon 20 insertion compared to patients with common mutations, survival was not significantly lower, after adjusting for stage at diagnosis. A possible explanation for this, aside from a low patient number in the exon 20 insertion group, is that in early stage NSCLC, patients tend to be treated with surgery, radiation therapy, curative chemotherapy or a combination of these treatments, mostly irrespective of EGFR mutation status. These patients are not treated with EGFR TKIs unless they fail conventional therapies. A plateau in DFS was observed across all types of EGFR mutations, starting at approximately 48 months. This flattening of the KM-curve may indicate disease cure in a number of patients.

For advanced stage NSCLC patients, survival outcomes were worse in patients with exon 20 insertions compared to common mutations (mOS: 21.2 vs 32.2 months, first-line mPFS: 5.8 vs 12.7 months). In a recent analysis from Canada (Alberta), a shorter mOS (11.2 vs 15.9-20.8 months) and first-line PFS (4.4 vs 8.2-9.6 months) in exon 20 insertion patients compared to common mutations was found.[32] Very few exon 20 insertion patients were included (18 patients for OS and 13 for PFS), which created very wide confidence intervals. Moreover, patients in appeared to do worse in general. Another recent study from the USA comparing exon 20 insertions to common mutations observed more similar survival outcomes (mOS 16.2 vs 25.5 vs and first-line mPFS 5.1 vs 10.5 months).[33] Outcomes in both exon 20 insertion and common mutation patients appeared to be slightly worse compared to this analysis, but is mainly attributed to the fact that OS and PFS were calculated from the start of the first line of treatment instead of the advanced stage diagnosis date.

Recent studies suggest that complex EGFR mutations seem to provide better survival outcomes than single uncommon mutations.[33-35] A similar trend was observed in mOS (complex vs single uncommon, 30.0 vs 26.0 months) and first-line mPFS (complex vs single uncommon, 12.5 vs 10.4 months) in advanced stage patients in this analysis. However, very few patients (30-38 complex mutated patients) were identified for this analysis, making confidence intervals very wide. Moreover, complex mutations are a very heterogeneous group, composed of various combinations of individual mutations. Hence, determining which specific compositions of complex mutations respond well to specific EGFR TKIs remains unclear. Recent studies suggest that afatinib provided better survival outcomes in complex mutations and other uncommon mutations than first-generation EGFR TKIs.[38-40] This was not explored in this analysis, due to insufficient uncommon mutated patients that were started on afatinib.

The mPFS of first-line osimertinib was found to higher compared to first- and second generation TKIs (15.9 vs 12.0 months) in advanced stage, common mutated NSCLC patients. This value is lower than the mPFS found in a phase III trial comparing first-line osimertinib against first generation EGFR TKIs (mPFS 18.9 vs 10.2 months), as real world cohorts tend to have worse outcomes compared to trial populations.[6,36] In addition, a real-world cohort from the USA demonstrated an even lower mPFS (13.1 months) compared to this analysis. mPFS for patients treated with first- and second generation EGFR TKIs is in line with two other real-world Canadian studies (11.2-11.7 months), supporting our results.[32,37] The efficacy of osimertinib in uncommon mutations was not explored due to small sample size.

The frequency of the specific exon 20 insertions found in this analysis are similar to those found in a study from New York, USA.[41] Contrarily, an Australian analysis found completely different frequencies of specific exon 20 insertions.[29,42] This suggests that not only the prevalence of exon 20 insertions differs regionally, but also the specific subtypes. This may be relevant as there are indications that poziotinib provides better response in near-loop insertions compared to far-loop insertions.[43] Moreover, some case studies suggesting that afatinib has provided good response in specific insertions such as M766_A767insASV and A763_T764insFQEA, whereas overall response of afatinib in exon 20 insertion is considered to be poor.[38,42,44,45] One patient in this analysis with M766_A767insASV was treated with afatinib and had a good response.

Of all 18 EGFR-positive NSCLC patients that stopped due to toxicity while being treated with an EGFR TKI, five of these toxicities were drug-induced pneumonitis and three hepatotoxicity. Four out five patients with drug-induced pneumonitis were treated with osimertinib and all patients with hepatoxicities with gefitinib. Recent studies previously coupled an increased risk of these complications to these specific EGFR TKIs and this may be reflected in clinical practice.[46,47]

The limitations of the present study are common to those encountered in real-world, retrospective, relatively small sample-size, data analyses. Firstly, study data were derived solely from the Princess Margaret Cancer Centre, which is a centre that has a high level of expertise on treating patients with NSCLC. Conjointly, selection bias related to patients and local protocolized practice patterns cannot be excluded. Another Canadian analysis estimating EGFR prevalence found that EGFR positive patients was significantly higher at Princess Margaret Cancer Centre compared to other centres in Canada.[24] Secondly, essential parts of patient history (when patients were partially treated outside the Princess Margaret Cancer Centre) were missing. However, our results are reflective of real-life practice patterns and treatment choices as well as outcomes in a very rare patient population and therefore add relevant data. Thirdly, bias may be created due to the usage of centre-specific molecular testing platforms combined with a change in types of molecular platforms over the recent years. Nonetheless, a sensitivity analysis showed that the proportion of uncommon mutations compared to common mutations in the prevalence population did not change between 2015-2019 (*appendix 4*). Lastly, due to the low sample size in analyses involving EGFR uncommon mutations, uncertainties surrounding outcomes such as survival are very large, which makes interpretation and generalisability difficult.

In terms of generalisability, previous studies categorized uncommon mutations differently; for example, some combined exon 20 insertions and other uncommon mutations into one group. A similar inconsistency is observed concerning complex mutations. Some studies grouped single and complex mutations together, and others did not differentiate between the possible combinations of common and uncommon mutations or even excluded all complex mutations. Therefore, it may be difficult to compare current available evidence. Creating universal terms of uncommon and complex mutations in survival analyses in order to make more accurate comparisons is important.

This study underlines the need for new targeted therapies for patients harboring an exon 20 insertion in clinical practice. New drugs, amivantamab and mobocertinib, targeting exon 20 insertions specifically have shown promising results in phase 1 and 2 trials (in the second line, pretreated with platinum doublet).[48] Mobocertinib as a first-line drug is currently being assessed. Moreover, first-line poziotinib has demonstrated promising results in near-loop (A767-P772) exon 20 insertions.[17] Where this analysis demonstrated the benefit of first-line osimertinib compared to other EGFR TKIs in patients with common EGFR mutations, the efficacy of osimertinib in patients with uncommon mutations remains unknown. However, the Canadian trial OCELOT is currently assessing the efficacy of osimertinib in uncommon mutations.[9] Other uncommon mutations and complex mutations are heterogeneous groups that respond variable to EGFR TKIs. As previously mentioned, evidence suggests that different EGFR TKIs may respond differently to specific uncommon mutations.[15-17,20,21] Similarly, the different subgroups of complex mutations are likely to respond differently to EGFR TKIS.[33-35] However, in this single-site analysis patient numbers are very limited and before such specific sub-analyses can be generalized across Canada, other sites have to be included to increase sample size. Thus, this data has to be merged, once available, with data from other Canadian centres in the observational study CARMA-BROS. Ultimately, these results can help creating a real-world comparison arm to new treatments for uncommon EGFR mutations.

Conclusion

In this observational, retrospective cohort study, prevalence, demographics, treatment patterns and survival outcomes of EGFR-positive NSCLC patients were compared. Complex EGFR mutations and EGFR exon 20 insertions are the most frequent uncommon mutation amongst all uncommon mutations, with exon 20 insertions being particularly common amongst Caucasians and smokers. Advanced stage NSCLC patients with common mutations and other uncommon mutations appear to be treated similarly with mainly EGFR TKIs, while patients with exon 20 insertions were treated really differently with mainly platinum-based chemotherapy or trial treatment. Results suggest that advanced stage NSCLC patients with exon 20 insertions are doing worse in terms of survival compared to patients with other EGFR mutations. However, due to a small number of patients results have to interpreted with caution and therefore it is important to recruit more patient from different centres across Canada. These results will ultimately help creating real-world comparison arms in order to inform the clinical and reimbursement decisions of clinicians and payers, respectively, and in turn, may help improve clinical outcomes in these patients.

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Supplementary files

Appendix 1 – Difference in criteria used to select patient samples for analysis of prevalence (or proportion) of various EGFR subtypes and selection of patients for analysis of treatment and survival

Supplementary figure 1. Overview of different inclusion criteria for prevalence/demographics and for treatment and survival analysis. Criteria that were changed for the treatment and survival analysis are in red.

Inclusion prevalence/demographics:

- Patients ≥ 18 years
- Adenocarcinoma
- Diagnosed between January 1st 2015 and Dec 31st 2019
- Tested for both common and uncommon mutations

Inclusion treatment and survival analysis:

- Patients ≥ 18 years
- Patients with any subtype of NSCLC.
- Patients confirmed to have an EGFR mutation by any testing platform.
- Patients diagnosed at any time.

Appendix 2 – Distribution of complex mutations for treatment patterns and survival analysis

Complex mutation	Mutation 1	Mutation 2	Treatment group Sankey/Swimmer	Survival analysis
Double common	Common	Common	Common mutation	Complex mutation
Common + uncommon	Common	Uncommon	Common mutation	Complex mutation
Double uncommon (non-exon 20 insertion)	Uncommon	Uncommon	Uncommon mutation	Complex mutation
Exon 20 insertion + any	Exon 20 insertion	Common/uncommon	Exon 20 insertion	Complex mutation

Supplementary table 1. Distribution of complex mutations for treatment and survival analysis. Essentially, complex mutations were assigned to specific mutation that decided the treatment type. No triple mutations (other than acquired T790M or amplifications) were identified.

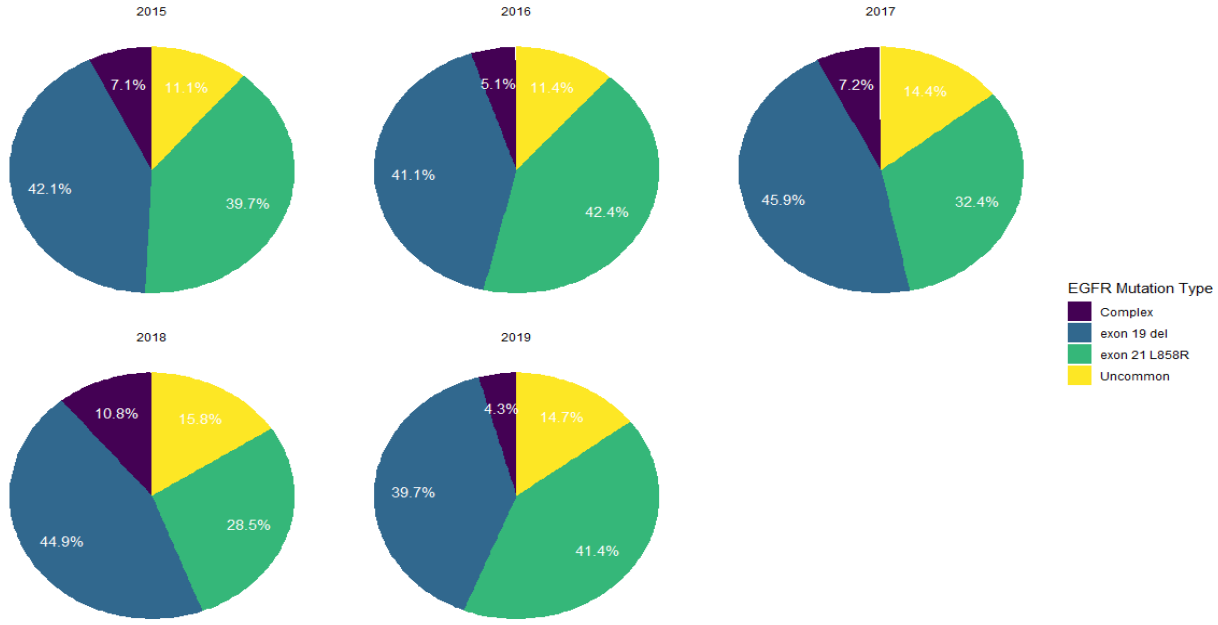
Appendix 3 – Frequencies of specific exon 20 insertions

label	levels	all	Total
Total N (%)		N = 73 (100.0)	N = 73
Exon20	A763_Y764insFQEA	1 (1.4)	1 (1.4)
	A767_V768dup	1 (1.4)	1 (1.4)
	A767_V769dup	5 (6.8)	5 (6.8)
	Exon 20 Insertion NOS	2 (2.7)	2 (2.7)
	H773_V774dup	3 (4.1)	3 (4.1)
	H773_V774insAH	2 (2.7)	2 (2.7)
	H773_V774insH	2 (2.7)	2 (2.7)
	H773_V774insNPH	1 (1.4)	1 (1.4)
	H773_V774insPH	1 (1.4)	1 (1.4)
	H773_V774insTH	1 (1.4)	1 (1.4)
	H773_V774insY	1 (1.4)	1 (1.4)
	M766_A767insASV	1 (1.4)	1 (1.4)
	N770_N771insGF	1 (1.4)	1 (1.4)
	N770_P772dup	1 (1.4)	1 (1.4)
	N771_P772insN	1 (1.4)	1 (1.4)
	N771delinsGY	1 (1.4)	1 (1.4)
	N771delinsHPH	1 (1.4)	1 (1.4)
	N771delinsHV	1 (1.4)	1 (1.4)
	P772_H773dup	2 (2.7)	2 (2.7)
	S768_A770dup	1 (1.4)	1 (1.4)
	S768_D770dup	11 (15.1)	11 (15.1)
	S768_V769delinsIL	1 (1.4)	1 (1.4)
	S768_V769insLDS	1 (1.4)	1 (1.4)
	unspecified	27 (37.0)	27 (37.0)
	V769_D770insGFV	1 (1.4)	1 (1.4)
	V769_D770insSSV	1 (1.4)	1 (1.4)
	V774_C775insHV	1 (1.4)	1 (1.4)

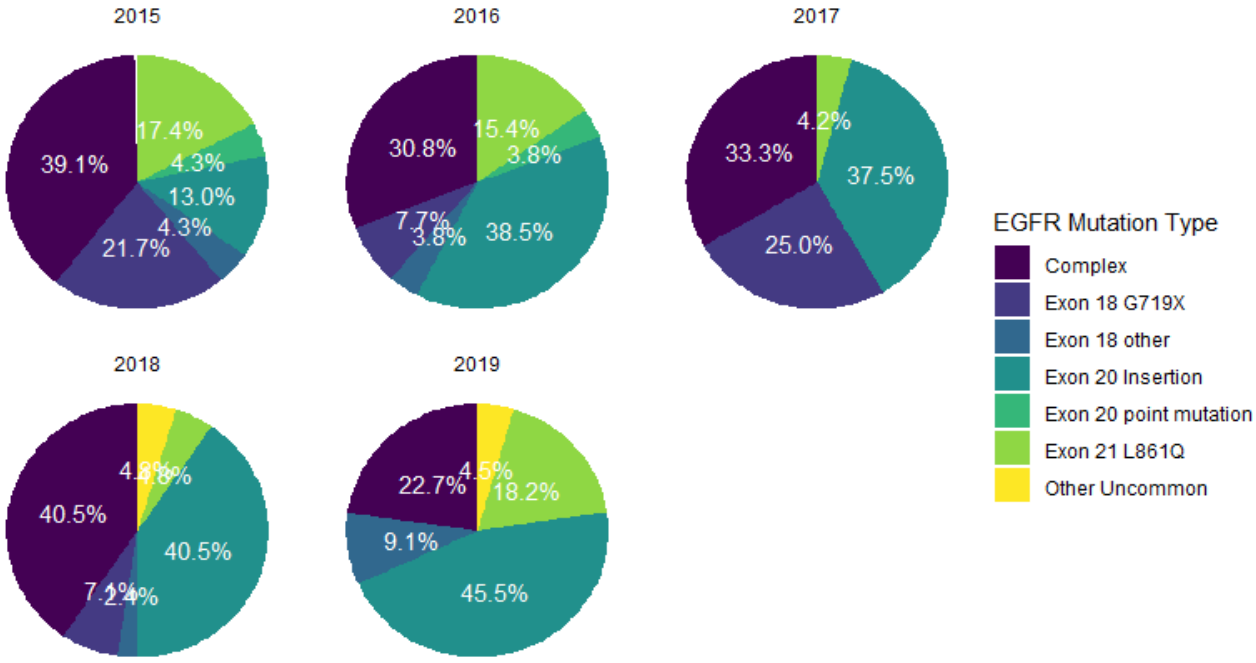
Supplementary table 2. Specific types of exon 20 insertions in NSCLC patients.

Appendix 4 – Yearly prevalence of EGFR mutations

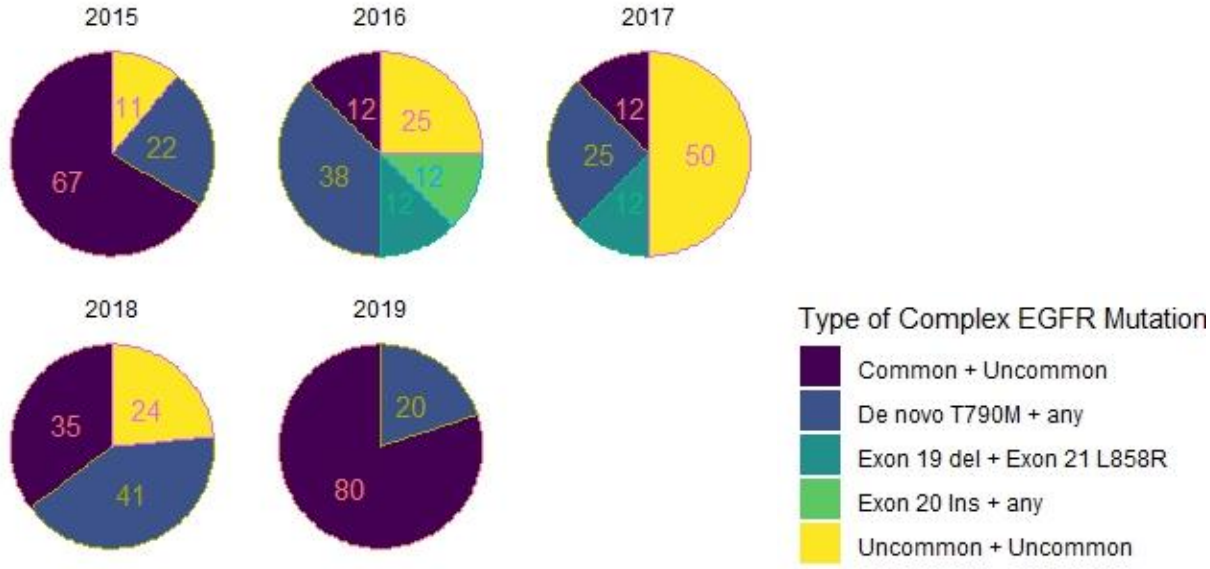
Supplementary figure 2A. Yearly prevalence of EGFR mutations in 669 adenocarcinoma patients diagnosed between Jan 1st 2015 and December 31st 2019. Total number of patients per year was 126 (2015), 158 (2016) 111 (2017) 158 (2018) and 116 (2019).



Supplementary figure 2B. Yearly prevalence of different types of uncommon and complex mutations in adenocarcinoma patients diagnosed between Jan 1st 2015 and December 31st 2019. Total number of patients per year was: 23 (2015), 26 (2016), 25 (2017), 41 (2018), 22 (2019).



Supplementary figure 2C. Yearly prevalence (%) of different types of complex mutations in adenocarcinoma patients diagnosed between Jan 1st 2015 and December 31st 2019. 9 (2015), 8 (2016), 8 (2017), 17 (2018), 5 (2019). Due to a low number of patients, percentages differed immensely per year.



Appendix 5 – Types of EGFR mutation stratified by year

label	levels	2015	2016	2017	2018	2019	Total	p
Total N (%)		N = 126 (18.8)	N = 158 (23.6)	N = 111 (16.6)	N = 158 (23.6)	N = 116 (17.3)	N = 669	
Type of EGFR mutation	18: g719a,	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.1)	0.149
	a147t	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.1)	
	Exon 18 G719X	5 (4.0)	2 (1.3)	6 (5.4)	3 (1.9)	0 (0.0)	16 (2.4)	
	Exon 18 G719X, Exon 20 point mutation	0 (0.0)	2 (1.3)	2 (1.8)	2 (1.3)	0 (0.0)	6 (0.9)	
	Exon 18 G719X, Exon 21 L861Q	1 (0.8)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	3 (0.4)	
	Exon 18 other	1 (0.8)	1 (0.6)	0 (0.0)	1 (0.6)	2 (1.7)	5 (0.7)	
	Exon 18 other, Exon 21 Other	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.1)	
	exon 19 del	53 (42.1)	65 (41.1)	51 (45.9)	71 (44.9)	46 (39.7)	286 (42.8)	
	exon 19 del, de novo T790M	0 (0.0)	2 (1.3)	1 (0.9)	1 (0.6)	1 (0.9)	5 (0.7)	
	exon 19 del, exon 21 L858R	0 (0.0)	1 (0.6)	1 (0.9)	0 (0.0)	0 (0.0)	2 (0.3)	
	exon 19 del, Exon 18 G719X	1 (0.8)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	2 (0.3)	
	exon 19 del, Exon 18 other	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	
	exon 19 del, Exon 20 point mutation	4 (3.2)	0 (0.0)	0 (0.0)	2 (1.3)	0 (0.0)	6 (0.9)	
	Exon 20 Insertion	3 (2.4)	10 (6.3)	9 (8.1)	17 (10.8)	10 (8.6)	49 (7.3)	
	Exon 20 Insertion,C535R	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	
	Exon 20 point mutation	1 (0.8)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	
	exon 21 L858R	50 (39.7)	67 (42.4)	36 (32.4)	45 (28.5)	48 (41.4)	246 (36.8)	
	exon 21 L858R, de novo T790M	2 (1.6)	1 (0.6)	1 (0.9)	6 (3.8)	0 (0.0)	10 (1.5)	
	exon 21 L858R, Exon 18 G719X	0 (0.0)	1 (0.6)	1 (0.9)	0 (0.0)	1 (0.9)	3 (0.4)	
	exon 21 L858R, Exon 18 other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.1)	
	exon 21 L858R, Exon 20 point mutation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.7)	3 (0.4)	

	exon 21 L858R, Exon 21 L861Q	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.1)	
	exon 21 L858R, Exon 21 Other	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.1)	
	Exon 21 L861Q	4 (3.2)	4 (2.5)	1 (0.9)	2 (1.3)	4 (3.4)	15 (2.2)	
	g779p	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.1)	
	r836h	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	1 (0.1)	

Supplementary table 3. Types of EGFR mutations found in adenocarcinoma patients between 2015 and 2019, stratified by year.

Appendix 6 – Demographics table with subgroup exon 20 insertion

label	levels	Complex	exon 19 del	Exon 20 Insertion	exon 21 L858R	Other Uncommon	Total	p
Total N (%)		N = 47 (7.0)	N = 286 (42.8)	N = 49 (7.3)	N = 246 (36.8)	N = 41 (6.1)	N = 669	
Age at Dx	Median (IQR)	66.1 (59.3 to 74.9)	65.9 (56.1 to 73.4)	63.1 (56.9 to 72.2)	69.4 (59.3 to 76.4)	70.2 (60.5 to 77.8)	67.0 (58.0 to 75.2)	0.042
sex	Female	30 (63.8)	189 (66.1)	37 (75.5)	173 (70.3)	28 (68.3)	457 (68.3)	0.605
	Male	17 (36.2)	97 (33.9)	12 (24.5)	73 (29.7)	13 (31.7)	212 (31.7)	
ethnicity	Asian	23 (60.5)	130 (59.4)	11 (29.7)	136 (71.6)	12 (50.0)	312 (61.4)	<0.001
	Caucasian	12 (31.6)	67 (30.6)	23 (62.2)	42 (22.1)	10 (41.7)	154 (30.3)	
	Other	3 (7.9)	22 (10.0)	3 (8.1)	12 (6.3)	2 (8.3)	42 (8.3)	
	(Missing)	9	67	12	56	17	161	
smoking_status	Current smoker	3 (6.4)	10 (3.6)	2 (4.1)	9 (3.8)	9 (22.5)	33 (5.1)	<0.001
	Ex-smoker	18 (38.3)	64 (23.3)	18 (36.7)	63 (26.4)	18 (45.0)	181 (27.8)	
	Never smoker	26 (55.3)	201 (73.1)	29 (59.2)	167 (69.9)	13 (32.5)	436 (67.1)	
	(Missing)	0	11	0	7	1	19	
Packyrs	Median (IQR)	13.0 (5.0 to 32.0)	20.0 (10.0 to 30.0)	15.0 (10.0 to 15.0)	20.0 (10.0 to 30.0)	30.0 (19.0 to 40.0)	20.0 (10.0 to 30.0)	0.114
Stage_at_dx	I	12 (25.5)	89 (31.2)	12 (24.5)	95 (38.6)	12 (29.3)	220 (32.9)	0.016
	II	4 (8.5)	14 (4.9)	3 (6.1)	7 (2.8)	4 (9.8)	32 (4.8)	
	IIIA	4 (8.5)	19 (6.7)	10 (20.4)	18 (7.3)	5 (12.2)	56 (8.4)	
	IIIB	2 (4.3)	8 (2.8)	1 (2.0)	5 (2.0)	4 (9.8)	20 (3.0)	
	IV	25 (53.2)	155 (54.4)	23 (46.9)	121 (49.2)	16 (39.0)	340 (50.9)	
	(Missing)	0	1	0	0	0	1	
Diagnosis Year	2015	9 (19.1)	53 (18.5)	3 (6.1)	50 (20.3)	11 (26.8)	126 (18.8)	0.171
	2016	8 (17.0)	65 (22.7)	10 (20.4)	67 (27.2)	8 (19.5)	158 (23.6)	

	2017	8 (17.0)	51 (17.8)	9 (18.4)	36 (14.6)	7 (17.1)	111 (16.6)	
	2018	17 (36.2)	71 (24.8)	17 (34.7)	45 (18.3)	8 (19.5)	158 (23.6)	
	2019	5 (10.6)	46 (16.1)	10 (20.4)	48 (19.5)	7 (17.1)	116 (17.3)	
ECOG at Initial Dx	>=2	3 (6.4)	11 (3.8)	2 (4.1)	9 (3.7)	1 (2.4)	26 (3.9)	0.318
	0	7 (14.9)	35 (12.2)	10 (20.4)	18 (7.3)	3 (7.3)	73 (10.9)	
	1	10 (21.3)	59 (20.6)	10 (20.4)	43 (17.5)	10 (24.4)	132 (19.7)	
	Unknown	27 (57.4)	181 (63.3)	27 (55.1)	176 (71.5)	27 (65.9)	438 (65.5)	

Supplementary table 4. Demographics and clinical characteristics of all EGFR-positive adenocarcinoma patients diagnosed between 2015-2019, stratified by exon 19 del, exon 20 insertion, exon 21 L858R, other uncommon, or complex mutation.

Appendix 7 – Population for treatment and survival analysis

label	levels	Common	Exon 20 Insertion	Other Uncommon	Total
Total N (%)		N = 588 (80.9)	N = 73 (10.0)	N = 66 (9.1)	N = 727
Age at Dx	Median (IQR)	65.7 (57.2 to 74.7)	63.2 (56.7 to 71.5)	70.4 (59.6 to 76.5)	65.8 (57.1 to 74.6)
sex	Female	405 (68.9)	52 (71.2)	42 (63.6)	499 (68.6)
	Male	183 (31.1)	21 (28.8)	24 (36.4)	228 (31.4)
ethnicity	Asian	289 (60.8)	19 (33.3)	24 (54.5)	332 (57.6)
	Caucasian	151 (31.8)	34 (59.6)	17 (38.6)	202 (35.1)
	Other	35 (7.4)	4 (7.0)	3 (6.8)	42 (7.3)
	(Missing)	113	16	22	151
smoking_status	Current smoker	22 (3.8)	2 (2.7)	11 (16.9)	35 (4.9)
	Ex-smoker	149 (25.7)	26 (35.6)	32 (49.2)	207 (28.9)
	Never smoker	408 (70.5)	45 (61.6)	22 (33.8)	475 (66.2)
	(Missing)	9	0	1	10
Packyrs	Median (IQR)	17.0 (10.0 to 30.0)	10.0 (7.0 to 15.0)	27.5 (13.8 to 40.0)	15.0 (10.0 to 30.0)
MORPHCAT	Adenocarcinoma	564 (95.9)	69 (94.5)	59 (89.4)	692 (95.2)
	Adenosquamous carcinoma	2 (0.3)	3 (4.1)	1 (1.5)	6 (0.8)
	Atypical carcinoid	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
	Large cell carcinoma	4 (0.7)	0 (0.0)	1 (1.5)	5 (0.7)
	NSCLC, NOS	5 (0.9)	0 (0.0)	4 (6.1)	9 (1.2)
	Other	1 (0.2)	0 (0.0)	1 (1.5)	2 (0.3)
	Squamous cell carcinoma	10 (1.7)	1 (1.4)	0 (0.0)	11 (1.5)
	To be Checked	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
Stage_at_dx	I	164 (27.9)	14 (19.2)	18 (27.3)	196 (27.0)
	II	28 (4.8)	5 (6.8)	9 (13.6)	42 (5.8)
	IIIA	43 (7.3)	13 (17.8)	10 (15.2)	66 (9.1)
	IIIB	18 (3.1)	2 (2.7)	6 (9.1)	26 (3.6)
	IV	335 (57.0)	39 (53.4)	23 (34.8)	397 (54.6)
initial_intent	Curative	244 (41.5)	33 (45.2)	38 (57.6)	315 (43.3)
	Palliative	344 (58.5)	40 (54.8)	28 (42.4)	412 (56.7)
Diagnosis Year	2000	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.1)
	2006	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.3)
	2008	5 (0.9)	0 (0.0)	0 (0.0)	5 (0.7)
	2009	4 (0.7)	0 (0.0)	0 (0.0)	4 (0.6)
	2010	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.3)
	2011	10 (1.7)	2 (2.7)	1 (1.5)	13 (1.8)
	2012	14 (2.4)	0 (0.0)	0 (0.0)	14 (1.9)
	2013	23 (3.9)	0 (0.0)	1 (1.5)	24 (3.3)

	2014	104 (17.7)	3 (4.1)	4 (6.1)	111 (15.3)
	2015	122 (20.7)	4 (5.5)	13 (19.7)	139 (19.1)
	2016	129 (21.9)	11 (15.1)	12 (18.2)	152 (20.9)
	2017	39 (6.6)	11 (15.1)	13 (19.7)	63 (8.7)
	2018	46 (7.8)	19 (26.0)	13 (19.7)	78 (10.7)
	2019	40 (6.8)	12 (16.4)	8 (12.1)	60 (8.3)
	2020	32 (5.4)	5 (6.8)	1 (1.5)	38 (5.2)
	2021	15 (2.6)	6 (8.2)	0 (0.0)	21 (2.9)
ECOG at Initial Dx	>=2	18 (3.1)	3 (4.1)	2 (3.0)	23 (3.2)
	0	62 (10.5)	15 (20.5)	5 (7.6)	82 (11.3)
	1	94 (16.0)	13 (17.8)	13 (19.7)	120 (16.5)
	Unknown	414 (70.4)	42 (57.5)	46 (69.7)	502 (69.1)

Supplementary table 5. Patients included with the specific inclusion criteria for the treatment and prevalence population. An extra 58 patients were included, which ensured inclusion of 727 EGFR-positive NSCLC patients.

Appendix 8 – Overview of treatment in curative NSCLC patients

label	levels	Common	Exon 20 Insertion	Other Uncommon	Total	p
Total N (%)		N = 244 (77.5)	N = 33 (10.5)	N = 38 (12.1)	N = 315	
surgery	No	44 (18.0)	7 (21.2)	11 (28.9)	62 (19.7)	0.282
	Yes	200 (82.0)	26 (78.8)	27 (71.1)	253 (80.3)	
curative_systemictherapy	No	165 (67.6)	14 (42.4)	21 (55.3)	200 (63.5)	0.010
	Yes	79 (32.4)	19 (57.6)	17 (44.7)	115 (36.5)	
curative_radiation	No	172 (70.5)	20 (60.6)	23 (60.5)	215 (68.3)	0.286
	Yes	72 (29.5)	13 (39.4)	15 (39.5)	100 (31.7)	

Supplementary table 6. Proportion of curative (early stage) NSCLC patients that received surgery, curative systemic therapy or curative radiation treatment (yes/no) amongst all curative patients, stratified by EGFR mutation type.

label	levels	Common	Exon 20 Insertion	Other Uncommon	Total
Total N (%)		N = 200 (79.1)	N = 26 (10.3)	N = 27 (10.7)	N = 253
TxType_surg	Bilobectomy	3 (1.5)	0 (0.0)	1 (3.7)	4 (1.6)
	Lobectomy	156 (78.0)	23 (88.5)	23 (85.2)	202 (79.8)
	Other	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.4)
	Pneumonectomy	3 (1.5)	2 (7.7)	0 (0.0)	5 (2.0)
	Wedge/segmental resection	37 (18.5)	1 (3.8)	3 (11.1)	41 (16.2)

Supplementary table 7. Types of surgery amongst all curative (early stage) NSCLC patients, stratified by EGFR mutation type.

label	levels	Common	Exon 20 Insertion	Other Uncommon	Total
Total N (%)		N = 79 (68.7)	N = 19 (16.5)	N = 17 (14.8)	N = 115
SystemicTxType_curative	Chemo/Immuno Combo therapy	7 (9.0)	4 (21.1)	1 (5.9)	12 (10.5)
	Chemotherapy	66 (84.6)	15 (78.9)	16 (94.1)	97 (85.1)
	Targeted treatment	3 (3.8)	0 (0.0)	0 (0.0)	3 (2.6)
	Trial treatment	2 (2.6)	0 (0.0)	0 (0.0)	2 (1.8)
	(Missing)	1	0	0	1

Supplementary table 8. Types of systemic treatment in curative (early stage) NSCLC patients amongst all curative patients that received treatment, stratified by EGFR mutation type.

Appendix 9 – Overview of treatment in palliative NSCLC patients

label	levels	Common	Exon 20 Insertion	Other Uncommon	Total	p
Total N (%)		N = 418 (80.4)	N = 55 (10.6)	N = 47 (9.0)	N = 520	
line1_yn	No	8 (2.0)	5 (10.9)	5 (11.9)	18 (3.8)	<0.001
	Yes	384 (98.0)	41 (89.1)	37 (88.1)	462 (96.2)	
	(Missing)	26	9	5	40	
Palliative_Radiation	No	175 (41.9)	16 (29.1)	16 (34.0)	207 (39.8)	0.138
	Yes	243 (58.1)	39 (70.9)	31 (66.0)	313 (60.2)	

Supplementary table 9. Patients that received a first line of treatment or palliative radiation (yes/no) amongst all advanced stage NSCLC patients.

label	levels	Common	Exon 20 Insertion	Other Uncommon	Total
Total N (%)		N = 384 (83.1)	N = 41 (8.9)	N = 37 (8.0)	N = 462
line2_yn	Line 1 Ongoing	65 (16.9)	0 (0.0)	6 (16.2)	71 (15.4)
	No	67 (17.4)	3 (7.3)	9 (24.3)	79 (17.1)
	Unknown	27 (7.0)	4 (9.8)	3 (8.1)	34 (7.4)
	Yes	225 (58.6)	34 (82.9)	19 (51.4)	278 (60.2)
line3_yn	Line 1 Ongoing	65 (16.9)	0 (0.0)	6 (16.2)	71 (15.4)
	Line 2 Ongoing	31 (8.1)	4 (9.8)	0 (0.0)	35 (7.6)
	No	117 (30.5)	13 (31.7)	12 (32.4)	142 (30.7)
	Unknown	53 (13.8)	6 (14.6)	6 (16.2)	65 (14.1)
	Yes	118 (30.7)	18 (43.9)	13 (35.1)	149 (32.3)

Supplementary table 10. Patients that received second- or third line of treatment (yes/no) amongst all advanced stage NSCLC patients.

label	levels	Common	Exon 20 Insertion	Other Uncommon	Total	p
Total N (%)		N = 384 (83.1)	N = 41 (8.9)	N = 37 (8.0)	N = 462	
TxType_1	Chemo/Immuno Combo therapy	0 (0.0)	3 (7.3)	0 (0.0)	3 (0.6)	<0.001
	Chemotherapy	19 (4.9)	14 (34.1)	4 (10.8)	37 (8.0)	
	Immunotherapy	1 (0.3)	3 (7.3)	0 (0.0)	4 (0.9)	
	Targeted treatment	335 (87.2)	8 (19.5)	31 (83.8)	374 (81.0)	
	Trial treatment	29 (7.6)	13 (31.7)	2 (5.4)	44 (9.5)	

Supplementary table 11. Specific type of systemic treatment amongst all advanced stage NSCLC patients that received systemic treatment, stratified by EGFR mutation type.

Appendix 10 – Patients with exon 20 insertions treated with first-line afatinib

Patient	Specific insertion	Drug	PFS (months)	OS (months)
1	N771delinsHV	Afatinib	3.4	32.0
2	unspecified	Gefitinib	1.0	24.0
3	unspecified	Afatinib	4.3	10.3
4	M766_A767insASV	Afatinib	7.5	17.0
5	S768_V769insLDS	Afatinib	26.8	55.3
6	S768_V769delinsIL	Afatinib	0.9	24.0
7	unspecified	Afatinib	5.7	36.3
8	H773_V774insAH	Afatinib	4.2	6.0

Supplementary table 12. Patients with exon 20 insertions that received afatinib in the first-line setting.

Appendix 11 – Reasons for stopping in first-line of treatment in palliative NSCLC patients

label	levels	Common	Exon 20 Insertion	Other Uncommon	N = 462
Total N (%)		N = 384 (83.1)	N = 41 (8.9)	N = 37 (8.0)	10 (2.4)
Reason for stopping	Completed therapy as planned	5 (1.4)	3 (7.3)	2 (6.1)	31 (7.3)
	Death	28 (8.0)	1 (2.4)	2 (6.1)	10 (2.4)
	Stopped due to Comorbidties/complications	9 (2.6)	0 (0.0)	1 (3.0)	243 (57.4)
	Stopped due to Progression	194 (55.6)	31 (75.6)	18 (54.5)	45 (10.6)
	Stopped due to Toxicity	37 (10.6)	4 (9.8)	4 (12.1)	56 (13.2)
	Tx ongoing at last follow-up	51 (14.6)	0 (0.0)	5 (15.2)	28 (6.6)
	Unknown/Other	25 (7.2)	2 (4.9)	1 (3.0)	39
	(Missing)	35	0	4	N = 462

Supplementary table 13. Reasons for stopping first-line of treatment in advanced stage NSCLC patients.

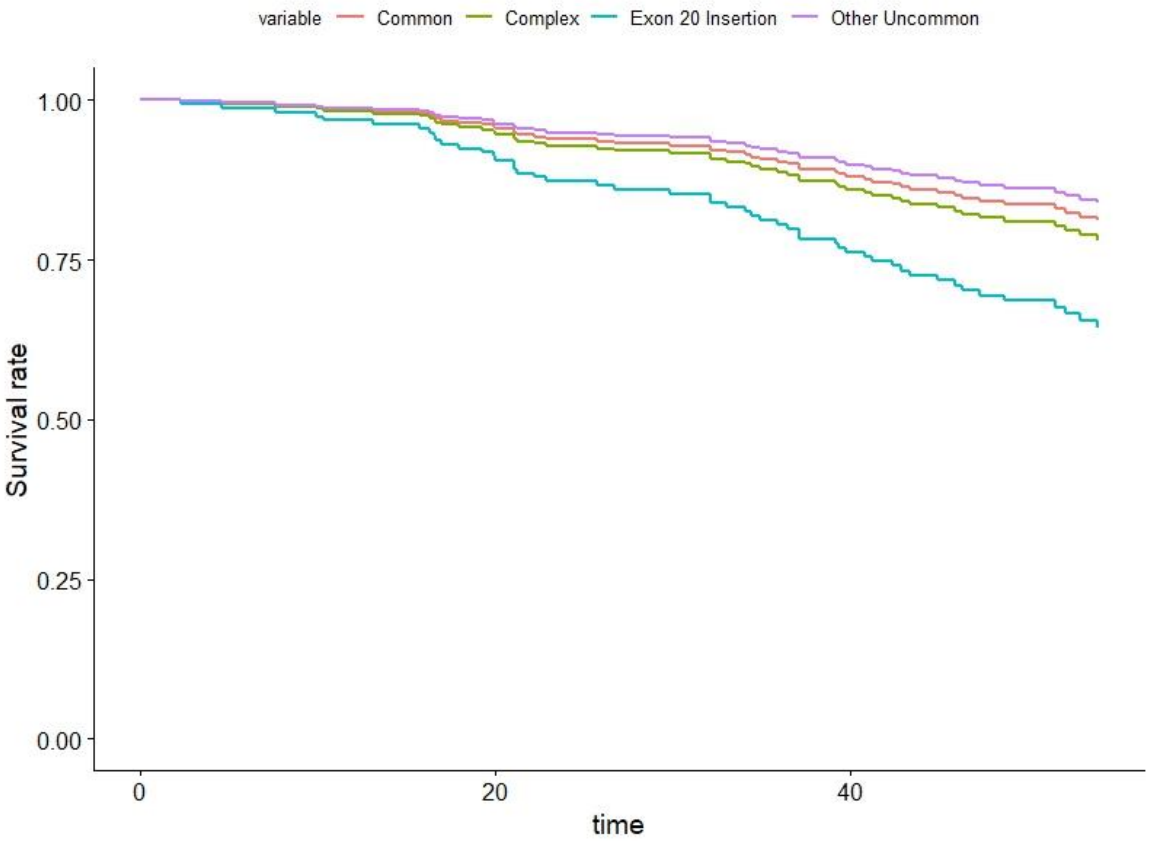
Appendix 12 – Patients harboring any EGFR mutation that stopped due to an EGFR TKI toxicity

Patient	Drug	Progression	Specific toxicity
1	osimertinib	Yes	Drug-induced pneumonitis
2	Mobocertinib	No	Drug-induced colitis (hospitalization)
3	poziotinib	No	Skin
4	Poziotinib	Yes	Skin
5	Poziotinib	Yes	Hypersensitivity pneumonitis, mucositis, rash, diarrhea
6	Gefitinib	Yes	Hepatotoxicity
7	mobocertinib	Yes	Diarrhea (hospitalization)
8	Gefitinib	No	Hepatotoxicity
9	Gefitinib	No	Skin and GI
10	Osimertinib	Yes	Drug-induced pneumonitis
11	Osimertinib	Yes	Drug-induced pneumonitis
12	Osimertinib	No	Drug-induced pneumonitis
13	Gefitinib	Yes	Skin
14	Gefitinib	Yes	Hepatotoxicity
15	Afatinib	Yes	Skin
16	Erlotinib	Yes	Unknown
17	Afatinib	No	Skin
18	Erlotinib	Yes	Skin

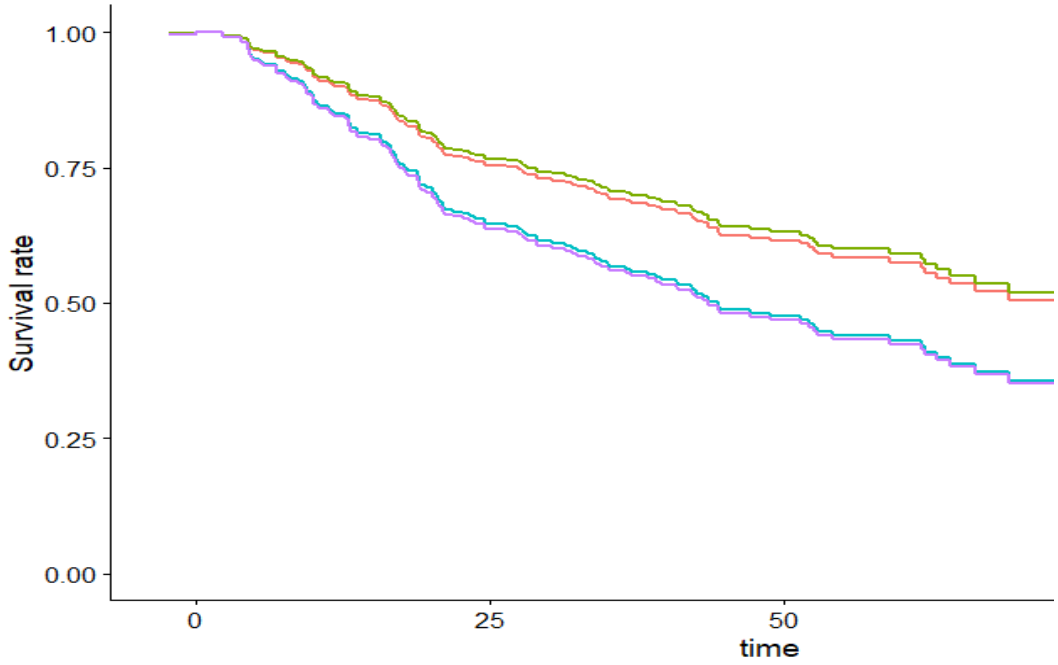
Supplementary table 14. Patients with any EGFR mutation that stopped EGFR TKI due to a toxicity. This table only included patients for which the main reason of stopping this line of treatment was due to a toxicity related to the specific EGFR TKI.

Appendix 13 – Cox proportional hazard model

Supplementary figure 3. Overall survival in early-stage NSCLC patients adjusted for stage at diagnosis, stratified by EGFR mutation type.



Supplementary figure 4. Disease-free survival in early stage NSCLC patients adjusted for stage at diagnosis, stratified by EGFR mutation type.



Appendix 14 - Exon 20 insertion patients receiving first-line poziotinib

Patient	Specific exon 20 insertion	PFS (months)	Reason for stopping
1	p.his773_val774dup	5.8	Due to progression
2	insertion	3.7	Due to progression
3	p.his773_val774insthrhis	24.0	Due to progression
4	p.ser768_asp770dup)	5.0	Due to progression
5	p.ser768_asp770dup	2.6	Due to progression
6	s768_d770dup	11.1	Due to progression
7	p.his773_val774instyr	1.8	Due to progression
8	s768_d770dup	13.1	Due to progression

Supplementary table 15. Exon 20 insertions receiving poziotinib in the first line. Far loop insertions (red) according to literature would have worse outcomes compared to near loop (green).[17]