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Original Research

A population-based study describing characteristics, survival and the effect of TKI treatment on patients with EGFR mutated stage IV NSCLC in the Netherlands

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Abstract ***Introduction:*** Since 2011, treatment guidelines advise targeted therapy (tyrosine kinase inhibitor, TKI) for patients with activating epidermal growth factor receptor (*EGFR*) mutations (*EGFR*+) in non-small cell lung cancer (NSCLC). We describe characteristics, first line treatment and survival of patients diagnosed with *EGFR*+ NSCLC in a European population, focussing on age, gender and trends over time and compare to the whole group and *EGFR*-.

Methods: All patients with non-squamous NSCLC stage IV, diagnosed 2011–2018, were identified from the population-based Netherlands Cancer Registry (N = 31,291).

Results: Among all, 7.0% were registered to be *EGFR*+, with highest prevalence in females <40 years (16%). Median overall survival (OS) ranged from 3.5 months in the *EGFR*- group >65 years to 23.6 months in the *EGFR*+ group <50 years treated with TKI. Over time, OS for the whole group increased by 0.6 months, of which 33% due to TKI treatment in *EGFR*+. The increase was strongest in females <50 years, where median OS almost doubled to 12.4 months.

Abbreviations: NSCLC, Non-small cell lung cancer; TKI, Tyrosine kinase inhibitor; *EGFR*, Epidermal growth factor receptor; *EGFR*+, *EGFR* positive tested tumours; *EGFR*-, *EGFR* negative tested tumours; NCR, Netherlands Cancer Registry; IKNL, Netherlands Comprehensive Cancer Organisation; OR, Odds ratio; HR, Hazards ratio; CI, Confidence interval.

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In the *EGFR*+, multivariable hazard of death was most strongly associated with the use of TKI (HR 0.45(0.41–0.49)). Of the patients with *EGFR*+ this space need or not, 71% received TKI treatment. Being young reduced the hazard of death (HR 0.71(95%CI:0.59–0.85)) irrespective of treatment, while male gender increased the hazard of death (HR 1.22(95% CI:1.11–1.33)).

Conclusion: At population level, TKI treatment in patients with non-squamous NSCLC stage IV *EGFR*+ has very strong beneficial effects on outcome. Of the improvement in OS that was made over the years for the whole group, about one third seems to be attributed to TKI treatment in *EGFR*+ patients.

1. Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) is the most common form, accounting for about 80% of all cases. Over the past decades, *EGFR, ALK, BRAF, ROS1, MET, RET, NTRK, KRAS* and *HER2* genes harbour specific activating genomic aberrations such as point mutations, fusions and amplifications that warrant molecular screening in the NSCLC population given the high tumour responses. Novel therapies targeting specific signalling pathways have been developed and gradually implemented in clinical practice. Small-molecule tyrosine kinase inhibitors (TKI) that specifically target the epidermal growth factor receptor (*EGFR*) by signal blockage are given as a first-line treatment resulting in longer progression-free survival, improved health-related quality of life and decreased treatment-related side-effects compared to those who receive platinum-based chemotherapy [2–5]. To be effective, the targeted tumour needs to have activating mutations in the *EGFR* gene. Receiving *EGFR*-TKI without having an *EGFR* mutation can even lead to shortening of progression-free survival when compared to treatment with platinum-based chemotherapy in these patients [6].

In previous studies, *EGFR* mutations are detected in about 10–15% of White patients with advanced NSCLC and up to 50% of Asian patients [7–12]. Besides being more prevalent in people from Asian descent, more *EGFR* mutations are seen in women, non-smokers and those with adenocarcinoma histology [8,12]. Also, NSCLC tumours in young patients, defined as <50 years, more often harbour *EGFR* mutations than in older patients [13–15].

Since 2011, first-line treatment with *EGFR*-TKIs was implemented in the Netherlands [16]. Gradually, *EGFR* mutational testing has increased from 73% of non-squamous NSCLC tumours in 2013 to 81% in 2017 ([17–19]). Another Dutch population-based study compared different first-line TKI treatments in patients with *EGFR*+ between 2015 and 2017 [20] and found beneficial effects on overall survival. However, the effects on population level and how this evolved over the years remained to be explored.

Therefore, the aim of this large population-based study is to describe characteristics in patients diagnosed with *EGFR* mutations in clinical daily practice with a special focus on gender and age in the Netherlands, the proportion treated with and effect of first-line *EGFR*-TKI-targeted therapy on survival on population level and how this evolved over the years. To give a complete overview, we also described the stage IV non-squamous NSCLC group as a whole and compared the patients that were diagnosed with an *EGFR*-mutated tumour to the rest of the group.

2. Methods

Population-based data from the Netherlands Cancer Registry (NCR) were used, which is maintained by the Netherlands Comprehensive Cancer Organisation (IKNL). The NCR records data on all patients newly diagnosed with cancer in the Netherlands and covers >95% of all cancers diagnosed in the Dutch population of around 17 million inhabitants. Trained registry personnel actively collects data from medical records on patient characteristics, e.g. gender, date of birth, postal code, and tumour characteristics, e.g. date of diagnosis, tumour type, subsite (International Classification of Diseases for Oncology (ICD-O-3) [21] histology, stage (TNM classification edition 7 and 8 (from 2017)) [22], grade and first-line treatment. The quality of the data is high due to thorough training of the registration clerks and a variety of computerised consistency checks. Information on the vital status of the patients was obtained from the population registries network, which provides virtually complete coverage of all deceased citizens of the Netherlands. The follow-up data were complete until February 2021. We included all patients who were diagnosed between 1st January 2011 and 31st December 2018 with non-squamous type NSCLC and clinical stage IV disease. Patients who were diagnosed at autopsy were excluded. Only first-line treatments were

recorded and these were analysed according to treatment type, no analyses were performed according to drug type. Patients in clinical trials were also registered and if patients received a combination of treatments in the first line, all treatments were registered. There was no information available on *EGFR* mutation subtypes or testing procedure. To determine the amount of patients that were tested in the Netherlands during the study period previously reported data from Kuipers *et al.* and Koopman *et al.* were used [17–19].

Analyses were performed according to age at diagnosis dividing patients into three age categories (≤49, 50–64, and 65+ years) and gender. Patient and tumour characteristics were shown according to these age categories. Kaplan–Meier curves were calculated according to *EGFR* mutation status, age and gender and trends were calculated based on 2-year periods according to year of diagnosis. For additional analysis of portions *EGFR*+ according to gender and age, the age categories were further divided into ten-year intervals ranging from <40 to 80≥. Multivariable proportional hazards regression analyses were used to discriminate the independent risk factors for death. Analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC). P-values were 2-sided and $p < 0.05$ was considered significant.

3. Results

3.1. Total group

From 2011 to 2018, 37,568 patients were diagnosed with stage IV pathologically confirmed NSCLC in the Netherlands. After exclusion of 6276 patients with squamous cell carcinoma and 1 patient aged younger than 18. 31,291 patients remained for analyses.

3.2. Age effects on total group

Of the total cohort, 6% was aged below 50 years (Table 1). The youngest category (<50 years) consisted of more females (54% versus 40% in 65+) had a higher proportion of adenocarcinomas (80% versus 74%, respectively), slightly more often had an *EGFR* mutation (8% versus 7%, respectively) and had more often advanced disease stage, cT4, cN3, cM1B (Table 1). Furthermore, the number of organs with metastases was higher in younger patients. More specifically, in the youngest category, metastases were most common in brain and adrenal gland.

3.3. EGFR+ prevalence in the Dutch population

Of the 31,291 included patients, 2188 were initially diagnosed with an *EGFR* mutated (*EGFR*+) tumour (7%). The percentage of patients with *EGFR*+ established ranging from 6% in 2011 to 8% in 2014 and 2018. In the *EGFR*+ patient group compared to the total group; women (65% versus 45%) and metastases to bone, lung and pleura (51% versus 39%, 30% versus 24% and 32 versus 24%, respectively) are more common (Table 1).

3.4. EGFR+ prevalence according to sex and age

Among the *EGFR*+ group, 65% were females. Among females, the prevalence of *EGFR*+ was highest in patients younger than 40, in which 1 out of 6 was registered to have *EGFR*+ disease (Fig. 1). Among women, the prevalence was also high in the 70–79-year-old (13%). The highest prevalence in males was in the 40–49-year-old and was 7%.

Among the patients with *EGFR*+, 141 (6%) were younger than 50 years (Table 1). In this group, again, the majority was female.

3.5. Treatment in EGFR+ patients

Two-third of the patients with *EGFR*+ received TKI as a first-line treatment, which ranged from 82% in those ≤49 years to 68% in those aged 65 years and older (Table 2). Radiotherapy to metastatic organs was given to 45% in the youngest and 27% of the oldest of the *EGFR*+ patient group. Best supportive care was given to 3% and 19% of the youngest and oldest patients with *EGFR*+, respectively. Over time, the proportion of patients with *EGFR*+ that did not receive TKI treatment reduced in all age groups. In 2011–2012, 41% of *EGFR*+ registered patients did not receive TKI treatment as a first line treatment, in 2017–2018 this reduced to 22%. In 2017–2018, 13% of the youngest and 24% of the oldest patients with *EGFR*+ did not receive TKI treatment.

3.6. Survival

Median overall survival of the total group was 4.8 months and ranged from 7.7 months in the youngest patients to 3.8 months in those aged 65 and older (log rank, p-value <0.0001). For the patient group with *EGFR*+ (overall *EGFR*+ group, 15.7 months), survival according to age ranged from 21.5 months in the youngest to 13.6 months in the oldest group. In the patient group without *EGFR* mutation (*EGFR*-), this was 7.2 to 3.5 months, respectively (overall *EGFR*- group, 4.4 months).

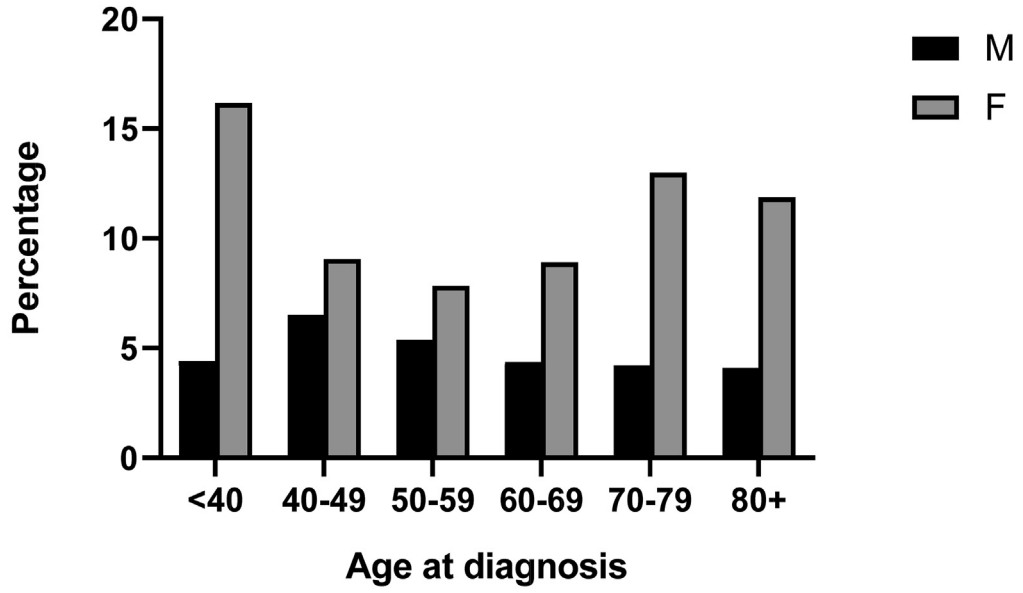
The longest survival was found in the *EGFR*+ group receiving TKI treatment. Median survival in the *EGFR*+ group with TKI treatment was 19.9 months overall, and 23.6 months in ≤49 years, 22.2 months in 50–64, and 18.7 months in those aged 65+ (p-value log rank: 0.0272) (Fig. 2A).

Patients who received best supportive care had a similar worse overall survival, with no significant differences according to age or *EGFR* mutational status. In

Table 1
Characteristics of patients diagnosed with stage IV non-squamous NSCLC 2011–2018, cytologically or pathologically confirmed in the Netherlands, according to age at diagnosis and presence of *EGFR* mutation.

	TOTAL					*EGFR*+				
	TOTAL	<50	50–64	65+	p-value@	TOTAL	<50	50–64	65+	p-value@
N (%)	31,291	1726 (5.5)	10,913 (34.9)	18,652 (59.6)		2188	141 (6.4)	712 (32.5)	1335 (61.0)	
Age mean (median)	66.9 (67)	44.6 (46)	58.4 (59)	73.8 (73)		66.9 (68)	44.3 (46)	58.2 (59)	74.0 (73)	
	%	%	%	%		%	%	%	%	
Sex										
Male	54.9	46.2	47.1	60.2	<0.0001	35.4	35.5	36.4	34.9	0.6
Female	45.1	53.8	52.9	39.8		64.6	64.5	63.6	65.1	
Histology										
Adenocarcinoma	75.7	79.6	77.2	74.4	<0.0001	91.6	93.6	91.3	91.5	0.4
Large cell	22.9	19.1	21.5	24.0		7.8	6.4	8.4	7.6	
Other &	1.5	1.3	1.3	1.6		0.6	0	0.3	0.8	
***EGFR* mutation**	7.0	8.2	6.5	7.2	0.0175					
cT stage										
0	0.8	0.8	0.9	0.8	<0.0001	0.6	0.7	0.8	0.5	0.4
1	12.8	13.3	14.2	12.0		11.9	13.5	11.7	11.8	
2	22.2	19.4	21.9	22.7		28.1	24.8	28.5	28.2	
3	17.7	18.7	17.6	17.6		14.9	17.0	14.3	14.9	
4	35.8	39.0	36.7	34.9		37.9	41.8	38.9	37.0	
X	10.7	8.8	8.8	11.9		6.6	2.1	5.6	7.6	
cN stage										
0	15.7	12.9	13.9	17.0	<0.0001	16.3	13.5	13.1	18.4	0.0006
1	6.1	5.4	5.9	6.3		6.3	2.8	6.2	6.7	
2	34.8	32.3	34.3	35.3		34.8	31.9	36.5	34.2	
3	37.2	45.5	41.9	33.7		37.7	48.9	40.6	35.0	
X	6.2	4.0	4.0	7.7		4.9	2.8	3.7	5.8	
cM stage#					<0.0001					
1A	23.1	16.2	17.2	27.2		25.6	20.6	19.0	29.7	<0.0001
1B	61.1	70.0	66.2	57.3		56.8	67.4	62.4	52.7	
1C	15.8	13.9	16.6	15.5		17.6	12.1	18.7	17.6	
Metastases[a]										
Bone	38.7	37.1	40.8	37.7	<0.0001	50.7	63.1	54.9	47.2	<0.0001
Adrenal gland	20.3	23.2	22.1	18.9	<0.0001	11.2	7.8	12.2	10.9	0.3
Liver	17.8	18.5	17.6	17.6	0.7	20.1	24.8	20.9	19.2	0.2
Lung	24.2	23.0	23.5	24.6	0.0561	29.5	37.6	30.9	27.9	0.036
Pleura	24.4	16.6	18.3	28.7	<0.0001	32.1	22.7	25.6	36.6	<0.0001
Brain	20.6	29.8	26.0	16.5	<0.0001	19.0	21.3	23.7	16.2	0.0001
Lymph nodes	13.2	16.6	15.1	11.8	<0.0001	9.8	12.1	9.7	9.7	0.7
Other	17.6	22.5	19.7	15.9	<0.0001	11.7	19.9	14.8	9.2	<0.0001
Number of organs with metastases										
Median	2.0	2.0	2.0	1.0		2.0	2.0	2.0	2.0	
1	49.3	45.5	46.1	51.5	<0.0001	44.7	36.9	39.9	48.1	<0.0001
2	27.2	25.8	28.0	26.8		30.3	23.4	33.6	29.2	
≥3	23.5	28.6	25.9	21.7		25.1	39.7	26.5	22.7	

[a] Combinations possible; #M1C was only possible from 2017 (TNM edition 8); & other morphology: consists mostly of adenosquamous carcinoma, pseudosarcomatous carcinoma, spindle cell carcinoma NNO, and pleiomorphic carcinoma. @ p-value represents p-value resulting from Chi-square test, i.e. distribution across cells is tested.



		<40	40-49	50-59	60-69	70-79	80+
MALE	*EGFR*+	4	46	137	247	244	97
	Total	91	707	2550	5661	5790	2371
FEMALE	*EGFR*+	16	75	258	452	451	161
	Total	99	829	3291	5071	3472	1359

Fig. 1. Percentage of patients with *EGFR* positive non-squamous NSCLC, according to gender and age, 2011–2018 the Netherlands. EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

the *EGFR*+ group, the median overall survival with best supportive care was 2.0 months (Fig. 2B).

Over time, median survival for the whole non-squamous group increased from 4.6 months in 2011–2012 to 5.2 months in 2017–2018 (Fig. 3A). Of this 0.6 month improvement, 0.2 month was due to *EGFR*+ TKI (33%). *EGFR*+ TKI added circa 10% to the median overall survival of the whole group ((OS whole group excl. TKI treated patients = 4.7 months)/(OS whole group 2017–2018 = 5.2 months)) in 2017–2018. In males, the net increase was 0.5 months compared to 0.9 months in females (to 4.5 and 6.3 months in 2017–2018, respectively, Fig. 3C,D). The effect was strongest in females aged <50 years, with median overall survival of 12.4 months in 2017–2018.

In the *EGFR*+ group, median survival increased by 6.2 months and even stronger effects were observed in those who received TKI treatment (median overall survival 22.9 months in 2017–2018, Fig. 3B). Small numbers of patients in the youngest *EGFR*+ group hampered further analyses.

In multivariable analyses, the use of TKI treatment was most strongly associated with reduced risk of death (0.47 (0.42–0.51)), compared to no TKI treatment (Table 3). Sensitivity analyses including performance status (available from 2015) showed that the effect of having a score of 2 or higher was associated with a HR of 2.48 (2.05–3.03), compared to a score of 0.

Table 2
Treatment of patients with *EGFR* mutated non-squamous non-small cell lung cancer in the Netherlands according to age group, 2011–2018.

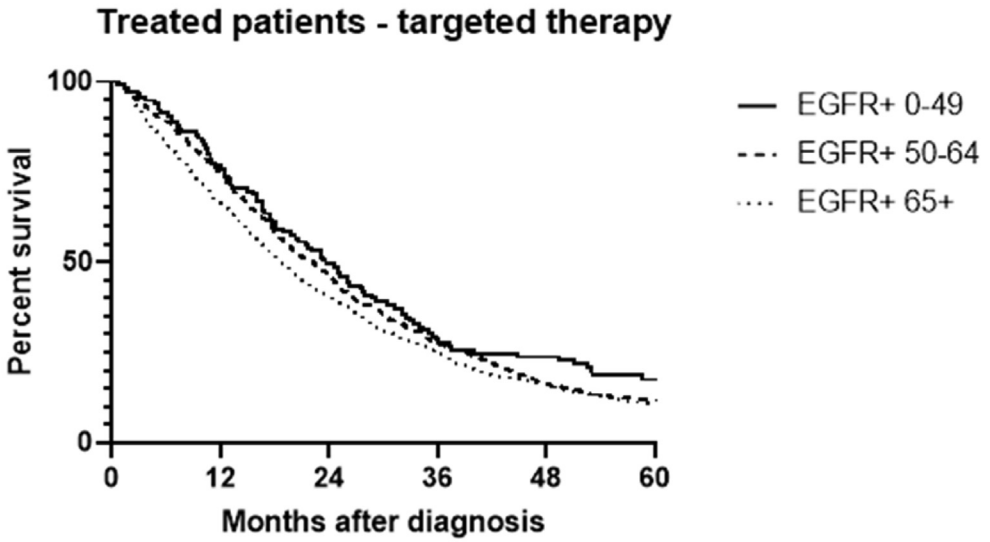
First line treatment#	Total	≤49	50–64	65+	p-value
Surgery					
Primary tumour	1%	1%	1%	1%	0.3
Metastasectomy	2%	3%	3%	1%	0.0087
Radiotherapy					
Primary tumour	4%	4%	4%	3%	0.5
Metastasis	31%	45%	37%	27%	<0.0001
Systemic therapy					
Chemotherapy	18%	26%	24%	14%	<0.0001
Chemoradiation	1%	2%	2%	1%	0.0038
TKI-treatment	71%	82%	74%	68%	0.0004
Immunotherapy	2%	2%	2%	1%	0.3
Best supportive care	14%	3%	8%	19%	<0.0001

Combinations possible (e.g. radiotherapy on metastasis and TKI treatment). # Sometimes chemotherapy is started awaiting the results of molecular analysis.

4. Discussion

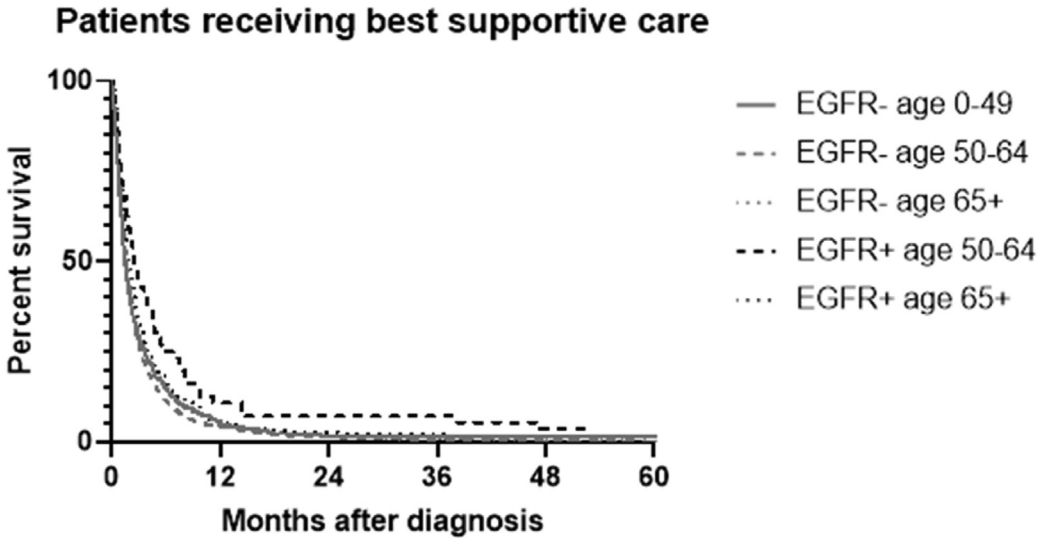
This population-based study shows that the use of TKI as first-line treatment strongly increased survival in *EGFR*+ stage IV NSCLC patients. This was independent of the improved survival that was seen over the

A.



Patients treated with TKI treatment as a first line treatment. P-value log rank= 0.0272.

B.



The total number of *EGFR+* patients receiving best supportive care in age group 0-44 was small (n=4), therefore data was not shown. P-value log rank <0.0001.

Fig. 2. Overall survival of patients with stage IV NSCLC, 2011–2018, the Netherlands, according to receiving targeted therapy versus best supportive care, *EGFR* mutation status and age at diagnosis. A. Patients treated with TKI treatment as a first-line treatment. P-value log rank = 0.0272. B. The total number of *EGFR*+ patients receiving best supportive care in age group 0–44 was small (n = 4), therefore data were not shown. P-value log rank <0.0001. EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

years and underlines the importance of testing for mutations in stage IV non-squamous NSCLC. During the study period still about one in five did not receive TKI as a first line treatment in the youngest group and TKI treatment was given even less in the older. Median OS ranged from 3.5 months in the *EGFR*- group over 65 years, to 23.6 months in the *EGFR*+ group with TKI treatment aged up to 50. Over time, median survival for

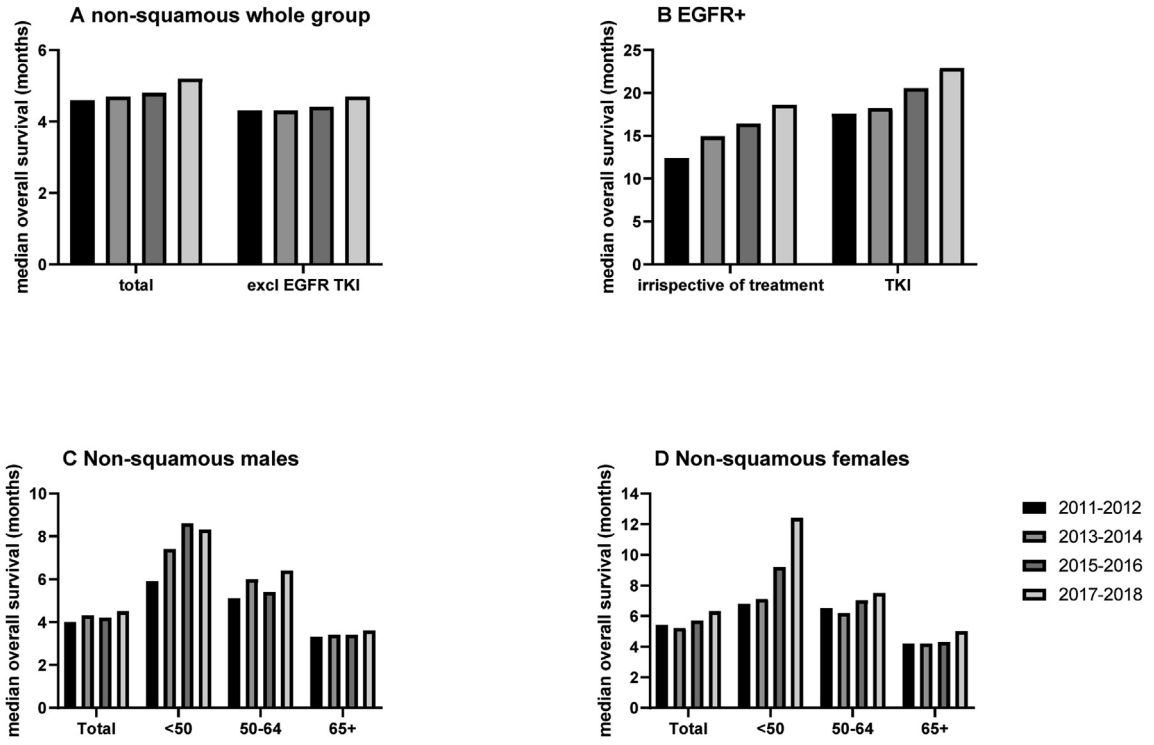


Fig. 3. Median survival of patients with non-squamous NSCLC according to 2-year periods, by gender and age in the Netherlands. Trends in median overall survival according to subgroup of non-squamous NSCLC and period of diagnosis, the Netherlands. A: total group of non-squamous including and excluding *EGFR*+ TKI (both p-log rank: <0.0001); B: *EGFR*+ total and TKI (both p-log rank: <0.0001); C: males total and age groups (p-log rank: <0.0001, 0.0002, <0.0001 and < 0.0001, respectively); D: females total and age groups (all p-log rank: <0.0001). EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor.

Table 3
Multivariable Cox regression analyses of survival of patients with non-squamous NSCLC, *EGFR*+, in the Netherlands, 2011–2018.

	HR	95%CI
Age		
0–49	0.70	0.58–0.84
50-64	0.76	0.69–0.83
65+	1.0	
Sex		
Male	1.22	1.11–1.34
Female	1.0	
Year of diagnosis	0.96	0.94–0.98
TKI-treatment		
Yes	0.47	0.42–0.51
No	1.0	

the whole non-squamous group slightly increased with an important contribution of *EGFR*+ TKI: 33% of the improvement was due to TKI. The effect was most strong in females aged less than 50 years where overall survival almost doubled to a median of 12.4 months in 2017–2018.

Treatment in the *EGFR*+ group was associated with age. Patients under 50 received significantly more specialised treatments like TKI, more treatments targeting metastases and less 'best supportive care'. In the clinical setting, we seem inclined to go further for younger patients. The data show, however, that all age groups benefit strongly from TKI treatment. Despite an improvement over time, the proportion of the *EGFR*+ group receiving TKI's is only 71% overall, ranging up to 82% in the youngest, meaning that still about one in 5 does not receive TKI treatment as first-line treatment in most recent years. Unfortunately, we had no information on reasons for not starting TKI treatment. Fourteen percent of *EGFR*+ received best supportive care, which likely results from patients being not fit enough or refusing tumour directed treatment. This seems also the reason for similar overall survival rates in *EGFR*+ and *EGFR*- groups when receiving best supportive care.

Furthermore, not starting TKI might be associated with molecular testing. Testing for EGFR mutations has been standard-of-care in the Netherlands since 2011, but next generation sequencing for *EGFR* has gradually been implemented into the routine setting for non-squamous NSCLC [18]. Although, the Netherlands is a small western country with easy access to care, especially in the early years of study patients might have chosen for other first-line treatments due to limited availability of EGFR testing or treatment near their home. A previous Dutch study found a median time between diagnosis and the start of TKI treatment to be 25 days in 2015–2017 [20]. In clinical practice, there can be a relatively long time between the test date and the result date and chemotherapy might be started as a first-

line treatment awaiting the results of mutational status. The urge to start might be especially high in patients with fast growing tumours or those with a poor performance score.

The prevalence of patients registered with *EGFR*+ and with non-squamous NSCLC stage IV was associated with age and gender. Proportions ranged from 8% in those aged ≤49 to 7% in 65+. Increasing age was associated with decreasing prevalence of *EGFR* mutations, which is in line with other studies [13–15]. However, based on the literature, we expected a higher proportion of patients with *EGFR*+, as 10–14% was found in the general Caucasian population with NSCLC and even up to 20–30% in the youngest group in previous studies [7–15]. Previous Dutch studies found that *EGFR* mutational status was tested in 73% of non-squamous NSCLC tumours in 2013, 79% in 2015 and 81% in 2017 in the Netherlands [17–19]. It is likely that at least part of the difference between our findings and other literature is due to underdiagnosis.

To detect *EGFR* mutations, currently, sampling of tumour tissue is necessary. And, although routinely performed, not all patients are eligible for this invasive procedure of tissue sampling. Furthermore, the procedure presents substantial challenges such as limited tissue availability or intra-tumour and inter-tumour heterogeneity [23,24]. It is likely that the proportion of tested patients will increase with the use of liquid biopsies. If 73–81% of all histologically proven patients with non-squamous NSCLC in this study were tested, we would have found *EGFR*+ in about 9.6% and 8.6% in case of a testing percentage of 100%, respectively, still less than could be expected in the Caucasian population according to the currently available literature [7,8].

To overcome the limitations of biopsy, testing of liquid biopsy samples is a promising development over the past decades. For this, the samples can consist of almost all body fluids and allow the extraction of circulating tumour DNA [25]. Although tissue testing is still the gold standard, recent studies show promising results and many laboratories are implementing liquid biopsy testing into research and diagnostic setting [26–28]. These new techniques make *EGFR* testing less invasive and clinically possible in (almost) all patients with NSCLC. Hopefully, this will lead to higher testing rates in the near future.

Biopsy necessity for *EGFR* testing might explain why more *EGFR* mutations were found in the young as they are more often fit enough to undergo biopsy. Also, doctors may be more eager to find mutations in the young. A more thorough search among the young was reported by earlier studies [17,29,30]. Young patients with NSCLC had a better prognosis in this study, also after correcting for TKI treatment, confirming the outcome of most studies [15,31–33]. But there has been conflicting data about survival in the young. Some studies have shown prognosis to be worse in the younger population indicating a more aggressive disease(13), and others have shown no difference in survival [34]. Good performance status was reported to be strongly associated with a reduced hazard of death [20,35]. In our study, the performance score was only available from 2015. Nevertheless, sensitivity analyses showed that the effect on survival was of similar (inverse) magnitude as the use of first-line TKI.

There were more women in the *EGFR*+ group, and female gender also reduced the hazard of death in this group. Other studies found similar results [8,36,37]. It is not completely clear whether young female patients with NSCLC are more often tested for *EGFR* mutations and treated with TKI's or if they have more *EGFR*+ tumours and respond better to therapy and it could be both. As this group seems to benefit most, 100% testing percentages should be aimed for.

In this study, patients with *EGFR*+ had more affected metastatic organs, especially bone, lung and pleura. The young patients had more brain metastases than the older group and only the incidence of pleural metastases significantly increased with age. Finding more brain metastases in the young was also described in previous reports [15,38,39]. It is likely that finding more metastases in *EGFR*+ as well as in younger patients is a result of a more thorough diagnostic search. Also, younger patients might present later in their disease course. Other studies have described that more brain metastases occur in patients with driver mutations such as *EGFR* [40,41] but this was not observed in our study.

A limitation of this study is that we only have information on *EGFR* mutation status at the time of initial cancer diagnosis. This might cause an under estimation of the *EGFR*+ group as some patients might have been tested later on. We expect this effect to be small as first line treatment with *EGFR*-TKI was already part of the national guidelines in 2011 and mutational status testing is done on diagnostic tissue. Unfortunately, only information on first-line treatment was available and information on follow-up was lacking. Accordingly, the amount of patients with *EGFR*+ that received TKI treatment from second line or later in the course of their disease might be underestimated. However, as first-line treatment with TKI was already part of the Dutch guidelines during the study period, it is likely that a significant proportion of these patients have not been treated with *EGFR*-TKI at all. Apart from that, the aim of the paper was to describe the impact of first line treatment on outcome.

In this study, we found a benefit on population basis of TKI treatment in patients with *EGFR* mutated tumours. It can be expected that similar results are found in patients treated with other molecular aberrations such as *ALK, RET* or *ROS* fusions. Numbers were too small

to include this in the present analyses. This will be the subject of future study.

In conclusion, we observed an increase in survival in patients with stage IV NSCLC over the years in clinical daily practice in the Netherlands. This was most strong in age groups <50, females and related to TKI treatment. TKI treatment contributed significantly to the improvement in survival of the whole group of stage IV non-squamous NSCLC. In this population, 7% were registered to have an *EGFR* mutation, but in 2017–2018, still 22% of them did not receive TKI treatment. Given the strong beneficial effects of *EGFR*-TKI treatment on outcome, it remains of utmost importance to perform molecular diagnostics and initiate treatment in all patients who are eligible for treatment.

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Credit author statement

Deirdre M.H.J. ten Berge: Methodology, Validation, Investigation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration. **Mieke J. Aarts:** Methodology, Validation, Formal analysis, Investigation, Writing – Original Draft, Writing - Review & Editing, Visualization. **Harry J.M. Groen:** Conceptualisation, Methodology, Writing - Review & Editing. **Joachim G.J.V. Aerts:** Methodology, Writing - Review & Editing, Supervision. **Jeroen S. Kloover:** Methodology, Writing - Review & Editing, Supervision.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: MJ Aarts reports grants from Amgen, outside the submitted work. HJM Groen reports other from Novartis, other from Eli Lilly, other from Merck, BMS, grants and other from Boehriger-Ingelheim, grants from Novartis, other from Roche, during the conduct of the study. JGJV Aerts reports personal fees and non-financial support from Msd, personal fees from Bms, personal fees from Boehringer-Ingelheim, personal fees from Amphera, personal fees from Eli-lilly, personal fees from Takeda, personal fees from Bayer, personal fees from Roche, personal fees from Astra zeneca, outside the submitted work; In addition, Dr. Aerts has a patent allogenic tumor cell lysate licensed to Amphera, a patent combination immunotherapy in cancer pending, and a patent biomarker for immunotherapy pending. The other authors have declared no conflicts of interest.

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