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Nationwide Real-world Cohort Study of First-line Tyrosine Kinase Inhibitor Treatment in Epidermal Growth Factor Receptor-mutated Non–small-cell Lung Cancer

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Abstract

Most trials regarding tyrosine kinase inhibitors in patients with advanced epidermal growth factor receptor-mutated non–small-cell lung cancer comprised selected series from Asian populations. We found that Western European patients with epidermal growth factor receptor-mutated non–small-cell lung cancer who received first-line treatment with regular tyrosine kinase inhibitors have a median overall survival of 20.2 months in our large nationwide real-world cohort. In patients with brain metastasis, erlotinib showed superior results compared with gefitinib and was similar to afatinib.

Background: Only a few randomized trials directly compared the relative efficacy of tyrosine kinase inhibitors (TKIs) in patients with advanced epidermal growth factor receptor (EGFR)-mutated non–small-cell lung cancer (NSCLC), and most trials comprised selected series from Asian populations. Therefore, the aim of this study was to assess the overall survival (OS) of advanced EGFR-mutated NSCLC in a large white population and to evaluate variation between different TKIs and identify predictors of survival. **Patients and Methods:** Information about clinical characteristics, treatment, and survival for 873 patients with stage IV EGFR + NSCLC, diagnosed from 2015 through 2017, was derived from the Netherlands Cancer Registry. OS was evaluated by actuarial analysis and multivariable Cox regression. Prognostic factors are reported as hazard ratios and 95% confidence intervals. **Results:** A total of 596 (68%) patients received first-line treatment with regular TKIs, providing a median survival of 20.2 months. Forty-five percent of patients were 70 years and older, and 54% of patients had distant metastasis in multiple organs. In the multivariate analysis, survival was significantly worse for men, and patients with higher age, poorer performance, and $\geq$ 3 organs with metastasis. Compared with erlotinib, OS was worse for gefitinib users (adjusted hazard ratio, 1.30; 95% confidence interval, 1.02-1.64), predominantly in patients with brain metastasis. **Conclusion:** Dutch patients with EGFR-mutated NSCLC who received first-line treatment with regular TKIs have a median OS of 20.2 months in a nationwide real-world cohort. In patients with brain metastasis, erlotinib showed superior results compared with gefitinib and was similar to afatinib.

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Keywords: Afatinib, Brain metastasis, Erlotinib, Gefitinib, Overall survival

Introduction

Non–small-cell lung cancer (NSCLC) remains the most common cause of cancer-related death worldwide, despite the rapid development of new therapies.[1] For NSCLC harboring an epidermal growth factor receptor (EGFR) mutation, first- (erlotinib, gefitinib) and second-generation (afatinib, dacomitinib) tyrosine

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kinase inhibitors (TKIs) resulted in a significant higher response rate and prolonged progression-free survival (PFS) in randomized clinical trials compared with standard chemotherapy, but overall survival (OS) did not differ.[2] Recently, the third-generation EGFR TKI osimertinib was registered as first line treatment of EGFR-mutated NSCLC, which showed a prolonged OS compared with standard TKIs.[3]

Direct head-to-head comparisons of the different first- and second-generation EGFR TKIs are scarce. A meta-analysis that summarized direct analysis between gefitinib and erlotinib showed no difference in OS. Also, the OS in the subgroup of patients with cerebral metastasis (6 studies; 303 patients) did not differ between treatments with erlotinib or gefitinib, as these drugs hardly pass the blood-brain barrier.[4] As first-line treatment, a direct comparison between gefitinib and afatinib showed no difference in OS and PFS, except for a small subgroup of long-term responders. In patients with cerebral metastasis, this study showed no differences in OS.[5] Another study reviewed results in patients with uncommon EGFR mutations and concluded that afatinib tends to perform better than first-generation TKIs.[6] This was also found in a large retrospective Canadian population-based study.[7]

Although it is clear that TKIs are effective in treatment of EGFR-mutated NSCLC, when extrapolating data from clinical trials to our (mainly white[8]) patients, a number of difficulties arise. The incidence of EGFR mutations differs across the globe, with a higher rate in Asians (47%) than in patients from the United States (22%) and Europe (15%).[9] Moreover, the relative frequency of various EGFR mutations (exons 18 through 21) tends to vary across continents.[10,11] Most trials evaluating EGFR TKIs were performed in Asia.[2] Only a few studies were performed in a European cohort, showing that treatment with TKIs improved PFS, but could be more effective in Asian populations.[12,13]

A second limitation is that results from clinical trials cannot be directly extrapolated to a general population, as outcomes are generally assessed in a highly selected population of relatively fit and younger patients or excluding patients with (symptomatic) brain metastasis.[14,15] A recent study by Cramer et al shows that survival in real-world surveys is nearly one-quarter shorter than for patients in clinical trials.[16]

Therefore, the primary aim of this study was to assess contemporary OS of Dutch patients (a mostly white population) with stage IV EGFR-mutated NSCLC in order to compare the outcome with international real-world series. The secondary aim was to identify predictors of survival as age, performance score, type of TKI, and disease characteristics such as the location of metastasis.

Patients and Methods

Data and Procedures

This is a retrospective, non-interventional, population-based study from the Netherlands. The Netherlands has a population of 17 million inhabitants, mainly white and including approximately 6% from Asian descent.[8] All patients diagnosed with any type of cancer are registered in the Netherlands Cancer Registry (NCR). A standardized dataset is collected from patient records consisting of basic patient and disease characteristics, including histology, TNM stage, World Health Organization (WHO) performance score (PS), site(s) of metastasis, and type of first-line treatment. Information on OS is obtained by annual linkage with the population registry. Data on treatment response, progression, second-line treatment, and cause of death is not available.

From the NCR, we selected all patients diagnosed between January 1, 2015 and December 31, 2017, with stage IV NSCLC and having any EGFR mutation, excluding patients with complex multiple mutations (eg, EGFR + KRAS). Information on EGFR mutation subtypes and EGFR testing procedure was not available. Prior evaluation of pathology reports revealed that 79% of patients with advanced non-squamous NSCLC had been tested for EGFR in 2015.[17]

The primary endpoint of this study was OS, calculated from the day of starting TKI, with follow up until February 1, 2019. For the overview of general characteristics, OS was calculated from the day of diagnosis.

For the evaluation of the primary endpoint, the analysis was restricted to the patients who received primary treatment with then regularly available TKIs (gefitinib, erlotinib or afatinib). Patients treated with experimental agents (including osimertinib at that time) or for whom type of TKI was not recorded were excluded from the main analysis.

Considering its retrospective and non-interventional nature, this study does not require approval from an accredited medical ethics committee (MEC) or the Central Committee on Research involving Human Subjects (CCMO). However, the study has been reviewed and approved by the Privacy Review Board of the NCR (application number K19.125).

Literature Search

For comparing our results to other real-world observational studies, a global review of literature was performed using a combination of the following general keywords in PubMed: "lung cancer," "EGFR," "real world," and/or "observational."

Statistical Analysis

Categorical variables were tabulated and reported as proportions. Associations between categorical variables were tested for significance with the χ^2 test.

The Kaplan-Meier method was used to estimate median OS, including 95% confidence intervals (CIs). For patients treated by regular first-line TKI, prognostic factors were assessed by multivariable Cox regression, and results are reported as hazard ratios (HRs) with 95% CIs. Variation between TKIs was additionally assessed after stratification by organ of metastasis, controlling for gender, age, WHO PS, histology, and number of metastatic organs in multivariable Cox regression. To allow comparison with trial series, variation between TKIs was also assessed after exclusion of patients with brain metastasis. A P-value of $< 5\%$ was considered as significant.

Results

From 2015 through 2017, 873 patients were diagnosed with stage IV NSCLC and any EGFR mutation. General patient characteristics are shown in Table 1. Most patients were female (65%), and 45% were aged 70 years or older. In 590 (68% of all) patients a PS was recorded, with a PS of 0 to 1 in 482 (82%) patients. The median time between diagnosis and start of TKI treatment was 25

Table 1 General Characteristics of 873 Patients With EGFR Mutation

	N	%	Median OS,[a] mos	95% CI
Gender				
Men	304	34.8	15.7	13.1-18.3
Women	569	65.2	18.2	15.9-20.5
Age, y				
18-59	198	22.7	22.0	17.8-27.7
60-69	281	32.2	17.8	15.3-20.0
70-79	282	32.3	17.2	14.1-20.4
80+	112	12.8	7.4	4.8-11.3
WHO PS				
0	251	28.8	23.9	20.8-27.7
1	231	26.4	17.8	15.1-20.4
2+	108	12.4	7.0	4.3-11.1
Not specified	283	32.4	13.3	11.3-15.9
Histology				
Adenocarcinoma	790	90.5	17.9	16.1-19.6
Other	83	9.5	10.0	6.5-15.2
Number of metastatic organs				
1	401	45.9	19.8	16.9-24.716.6-22.78.5-12.5
2	256	29.3	20.1	
3+	216	25.7	10.4	
First-line treatment				
TKI	608	69.8	21.2	18.6-24.5
Chemotherapy	142	16.1	18.5	15.5-21.2
Other/BSC	123	14.1	2.7	2.0-3.8

Abbreviations: BSC = best supportive care; CI = confidence interval; EGFR = epidermal growth factor receptor; OS = overall survival; TKI = tyrosine kinase inhibitor; WHO PS = World Health Organization performance score.
[a]Calculated from date of diagnosis.

days. In 5 patients, start of TKI treatment was not recorded but imputed at 25 days.

Most (68%) patients received first-line treatment with a then regularly available TKI, whereas 141 (16%) patients received first line chemotherapy and 123 (14%) received other treatment or best supportive care only. The most common type of TKI was erlotinib (n = 320), whereas 177 patients received gefitinib and 99 afatinib. Twelve patients were treated with another or unknown type of TKI as first-line therapy and were therefore excluded. Use of afatinib was increasing during the study period.

The median survival from day of diagnosis was 20.2 months (95% CI, 17.8-23.2 months) for patients treated with a regular available TKI as first-line treatment (n = 596), 21.2 months (95% CI, 18.6-24.5 months) for patients treated with any TKI (n = 608), and 18.5 months (95% CI, 15.5-21.1 months) for patients treated with first-line chemotherapy (n = 142). For patients receiving best supportive care only, with or without palliative radiotherapy on the primary tumor or metastatic sites, median survival was only 2.7 months (95% CI, 2.0-3.8 months).

Fourteen (2.3%) patients died within 30 days after diagnosis. Survival was favorable for patients who were female, of younger age (<80 years), and those with a better PS (Table 2). Survival was inferior for patients with non-adenocarcinoma histology and those with 3 or more organs affected with distant metastasis. In comparison with erlotinib, survival for gefitinib (HR, 1.30; 95% CI, 1.02-1.64) was inferior according to multivariable analysis, whereas results for afatinib did not differ (HR, 1.24; 95% CI, 0.91-1.68). Two-year survival for gefitinib, erlotinib and afatinib was 43% (95% CI, 35%-51%), 47% (95% CI, 41%-52%), and 43% (95% CI, 31%-54%), respectively (Figure 1).

TKI preference was not significantly associated with organ or number of metastasis at baseline and is mainly determined by institutional preference and year of diagnosis. At baseline, bone metastasis was the most frequent site of metastasis (54%), whereas brain metastasis was diagnosed in 19% (Table 3). Variation in OS between TKIs was most prominent for patients with brain metastasis, showing median survival of 14.5 months (95% CI, 9.5-19.4 months), 15.0 months (95% CI, 6.5 months to not reached), and 26.1 months (95% CI, 18.6-37.1 months) for gefitinib, afatinib, and erlotinib, respectively. Compared with erlotinib, gefitinib tends to perform worse (adjusted HR, 1.30; 95% CI, 1.02-1.64), most prominently in patients with brain metastasis (adjusted HR, 2.50; 95% CI, 1.33-4.71). Statistical significance was also reached in patients with bone and lung metastasis (Table 4). After exclusion of patients with brain metastasis and controlling for the other parameters, OS results for erlotinib were no longer superior in the multivariate analysis (HR, 1.14; 95% CI, 0.88-1.48), suggesting that patients with brain metastasis were clinically responsible for this variation in efficacy.

Table 2 Prognostic Factors for Overall Survival Calculated From Start of Treatment in Patients Treated With First-line TKI According to Multivariable Analysis (N = 596)

	N	Median OS (95% CI), mos	HR	95% CI
Gender				
Men	200	17.6 (14.8-20.5)	1	–
Women	396	22.5 (19.0-26.1)	0.76	0.61-0.95
Age				
18-59	145	24.3 (19.7-28.9)	1	–
60-69	181	18.4 (15.6-24.3)	1.26	0.95-1.69
70-79	204	20.8 (15.7-27.0)	1.29	0.97-1.71
80+	66	14.5 (8.8-19.5)	2.00	1.40-2.88
WHO PS				
0	186	24.8 (21.0-31.6)	1	–
1	155	19.6 (16.1-24.3)	1.24	0.94-1.65
2+	69	12.5 (8.5-20.2)	1.67	1.17-2.39
NS	186	16.1 (13.2-23.2)	1.42	1.08-1.86
Histology				
Adeno	553	20.8 (18.3-24.1)	1	–
Other	43	11.5 (6.0-21.8)	1.47	1.01-2.14
Number of metastatic organs				
1	265	24.5 (19.7-27.8)	1	–
2	187	21.8 (19.0-29.0)	1.16	0.90-1.49
3+	144	12.5 (10.3-16.7)	1.98	1.53-2.56
TKI Type				
Erlotinib	320	21.8 (17.9-24.7)	1	–
Gefitinib	177	18.3 (14.7-25.5)	1.30	1.02-1.64
Afatinib	99	20.8 (15.4-24.3)	1.24	0.91-1.68

Abbreviations: CI = confidence interval; HR = hazard ratio; OS = overall survival; TKI = tyrosine kinase inhibitor; WHO PS = World Health Organization performance score.

Discussion

The present study reported the real-world treatment patterns and outcomes of patients with NSCLC harboring EGFR mutations in the Netherlands. A total of 596 patients received first-line treatment with regular TKIs with a median survival of 20.2 months. Survival was significantly worse for men and patients with higher age, poorer PS, and ≥ 3 organs with metastasis. Compared with erlotinib, we observed a poorer adjusted survival for gefitinib users, especially when diagnosed with brain metastasis at baseline.

To our knowledge, this study is the largest European real-world cohort of patients with advanced NSCLC with an EGFR mutation evaluating first-line TKI treatment(Table 5) and the first to report data from an entire country as this registry includes the data of all Dutch hospitals.

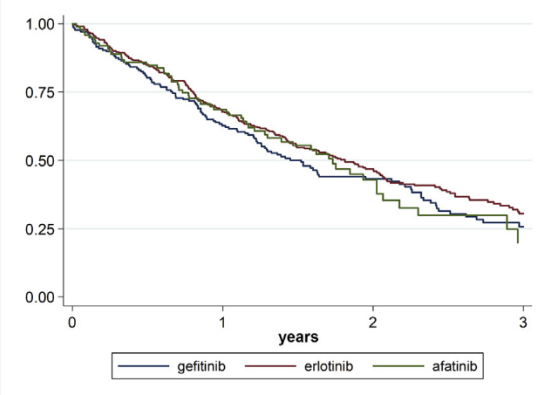
Compared with other large real-world observational studies (Table 5), our study is similar regarding the number of female patients and median age. Also, the median OS is comparable with most other European studies. The Asian studies tended to show a better OS, which is comparable with the clinical trials which are also mainly performed in Asia.[2] The real-world results of TKIs are inferior to those reported in clinical trials, probable because of less favorable patient characteristics such as a higher age or lower PS.[16]

One explanation for the difference in OS between European and Asian populations could be the variation in distribution of EGFR mutation subtypes. A number of studies showed a trend that patients with exon 19 deletions performed better than patients with a mutation in exon 21.[28] The latter occurs more often in European patients, next to a higher occurrence of non-sensitizing mutation of exon 20 and other rare mutations at baseline.[19,26] The incidence of these subtypes in the Netherlands is considered to be comparable with the data available from other referenced European studies, but specific data about subtypes were not available in the registry used in this study.[29] Another hypothesis would be that Asian patients respond better to TKI treatment owing to other, still unknown, biological differences.

As already known, in our study, higher age, male gender, poorer PS and ≥ 3 organs with metastasis were identified as negative predictors of survival.[19] Although the number of distant metastasis and involved organs is becoming more important in staging and subsequent survival according to the TNM eighth edition, this issue is often not routinely assessed in trial series. Also, these patients are often excluded from clinical trials.[14]

Against expectations, we observed that patients treated with erlotinib had a superior survival compared with patients treated with gefitinib, whereas there was no statistical difference to patients treated with afatinib. This difference disappeared when the patients with brain metastasis were excluded from the analysis with control for other factors, suggesting that this subgroup is clinically responsible. In a

Figure 1 Overall survival for Patients With Stage IV Non–small-cell Lung Cancer and Epidermal Growth Factor Receptor Mutation, Stratified by Type of Tyrosine Kinase Inhibitor



pooled analysis with 303 patients from 6 studies, OS was similar between patients treated with gefitinib or erlotinib.[4] There are no prospective trials directly comparing different TKIs in patients with brain metastasis. Speculating, this might be caused by a better blood-brain barrier passage of erlotinib compared with gefinitinib.[30] However, this finding should be considered as a post hoc observation, susceptible to small numbers and residual confounding parameters not included in the multivariate analysis (eg, WHO PS was missing in 31% of all cases, and information about symptomatology of brain metastasis is unknown). Also, information about (exon-)specific EGFR mutation type is lacking, and choice of TKI could be mutation-specific (for example, afatinib in uncommon mutations).[6,7]

When assessing the quality of the data presented herein, it is important to consider that in this study period, 79% of all Dutch patients with non-squamous NSCLC had been tested for EGFR, which is equal to high compared with other countries, which range from 43% to 85%.[17,31,32] Many patients received first-line chemotherapy as they were participating in the NVALT 17 trial (EudraCT Number: 2013-004303-39; no published results) comparing first-line monotherapy erlotinib versus 4 cycles of cisplatin/pemetrexed/erlotinib with subsequent maintenance pemetrexed/erlotinib in EGFR-mutated NSCLC. Also, several patients started with chemotherapy before a definitive assessment of EGFR status was performed to decrease treatment delay. The median OS was similar between patients who received a first-line TKI compared with those who started with chemotherapy. Former studies comparing TKIs with chemotherapy did not find a significant difference in OS, often attributed to crossover.[12]

As this is a cohort derived from a national registry, we were able to create a large study population without inclusion bias, as we included all stage IV NSCLC and only excluded patients with co-occurring mutations. As our patients are included from all hospitals in the country (eg, general, teaching, and university medical centers), we do not expect selection bias of TKI prescription by hospital type. But, as this is a retrospective registry, our dataset is limited to key data only, and information on therapy response and subsequent treatment is lacking. Second-line treatment could vary between hospitals, thereby causing bias when comparing the different first-line TKIs.

For patients diagnosed during 2015 to 2017, second-line osimertinib may have been used. Osimertinib has recently been approved by the European Medicines Agency (EMA) and soon will become first-line treatment for patients with EGFR-mutated NSCLC. Compared with erlotinib and gefitinib, osimertinib prolongs survival and has comparatively mild side effects.[3] This will change the standard EGFR TKI treatment in patients with EGFR mutations in favor of osimertinib. However, it is important to recognize that most patients in the control arm of the FLAURA trial were treated with gefitinib. The favorable effect of osimertinib might have been attenuated if more patients would have received erlotinib. Given the observational nature of our study, this remains speculation. Upfront treatment with osimertinib will lead to new resistance mutations as tumors escape to TKI treatment.[33] These new mutations show in vitro response to first- or second-generation TKIs, and therefore, the future of EGFR TKI development will involve evaluations of the patterns of distant metastasis after osimertinib, the spectrum of resistance mutations, and the role of local treatments for oligometastatic disease.[34] Novel EGFR TKIs will be developed along the novel mutations that will be found. However, osimertinib will not be approved or reimbursed in all countries in the world, and therefore, these data can help in guiding which TKI is the best treatment option.

Conclusion

In this Dutch nationwide population study, the median OS in patients with EGFR-mutated NSCLC treated with a first-line, first-

Table 3 Association Between Type of EGFR TKI and Organ of Metastasis at Baseline

	N	Erlotinib	Gefitinib	Afatinib	*P* Value
Overall	596	320 (53.7)	177 (29.7)	99 (16.6)	
Adrenal	63	36 (57.1)	17 (27.0)	10 (15.9)	.84
Bone	322	182 (56.5)	92 (28.6)	48 (14.9)	.28
Brain	112	65 (58.0)	29 (25.9)	18 (16.1)	.55
Liver	116	67 (57.8)	29 (25.0)	20 (17.2)	.46
Lung	185	96 (51.9)	54 (29.2)	35 (18.9)	.59
Pleural	216	109 (50.5)	71 (32.9)	36 (16.7)	.41

Abbreviations: EGFR = epidermal growth factor receptor; TKI = tyrosine kinase inhibitor.

Table 4 Prognostic Impact of Type of TKI, Adjusted for Other Prognostic Factors in Multivariable Analysis, Stratified by Organ of Metastasis[a]

Erlotinib	Gefitinib		Afatinib		
Reference	HR	95% CI	HR	95% CI	*P* Value
Overall	1.30	1.02-1.64	1.24	0.91-1.68	0.08
Adrenal	0.82	0.35-1.94	1.00	0.35-2.84	0.89
Bone	1.54	1.13-2.11	1.51	1.01-2.27	0.01
Brain	2.50	1.33-4.71	1.72	0.82-3.65	0.01
Liver	1.33	0.75-2.37	1.63	0.81-3.29	0.32
Lung	1.96	1.23-3.14	1.57	0.90-2.74	0.02
Pleural	0.85	0.58-1.25	.65	0.37-1.15	0.29

Abbreviations: CI = confidence interval; HR = hazard ratio; WHO PS = World Health Organization performance score.
[a]Controlling for gender, age, WHO PS, histology, and number of metastatic organs.

or second-generation TKI was 20.2 months, which is comparable with other European population-based studies but lower than that of Asian population-based studies. Higher age, male gender, poorer PS, and $\geq$ 3 organs with metastasis were associated with shorter survival. In patients with brain metastasis, erlotinib showed superior results compared with gefitinib and was similar to afatinib.

Clinical Practice Points

- The incidence of EGFR mutations differs across the globe, with a much higher incidence in Asia. Therefore, only a few studies evaluating EGFR TKIs were performed in small European cohorts. Although TKI treatment shows a prolonged PFS, there is no benefit on OS. A limited number of European population-based studies showed inferior survival of European patients compared with Asian patients.
- The present large cohort study reported the real-world treatment patterns and outcomes of mainly white patients with NSCLC harboring EGFR mutations in the Netherlands. We confirm the results of smaller cohorts and found that OS is comparable with other European population-based studies but lower than that of Asian population-based studies. We found that survival was significantly worse for men and patients with higher age, poorer PS, and $\geq$ 3 organs with metastasis. Compared with erlotinib, we observed a poorer adjusted survival for gefitinib users, especially when diagnosed with brain metastasis at baseline.

Table 5 Selected Review of Real-world Series Reporting Overall Survival for Patients With EGFR Mutation, Primarily Treated With TKIs

First Author	Origin	EGFR Mutation Types	N	Female, %	Median Age, y	Treatment	Survival, mos
Asia							
Fujiwara[18]	Japan	Exon 19 del or L858R	147	65	75	Gefitinib	27.3 (CI NS)
				61	72	Erlotinib	29.3 (CI NS)
Inoue[19]/Okamoto[20]	Japan	No exclusions	929	65	67	Gefitinib	28.5 (26.4-31.0)
Yao[21]	Taiwan	Excluded exon 20 insertions	226	65	65	Gefitinib	26.9 (21.2-32.5)
Shi[22]	China	No exclusions	463	54	62	Not stated	15 (13.1-16.9)
Xu[23]	China	Exon 19 del or L858R	141	61	63	Erlotinib/Gefitinib/Icotinib	30.7 (28.4-32.9)
Europe/North America							
Arriola[24]	Spain	No exclusions	187	62	71	Total	17.2 (13.5-21.4)
						Gefitinib	16.7 (12.4-20.1)
						Erlotinib	23.7 (15.2-31.5)
Remon[25]	Spain	No exclusions	318	100	65	Gefitinib/erlotinib	23.0 (19.8-26.2)
Schuette[11,26]	Germany	No exclusions	334	63	–	Any TKI	17.2 (15.1-19.8)
Li[27]	USA	No exclusions	593	68	69	Afatinib	20.7 (16.2-35.1)
			87			Erlotinib	23.2 (21.2-24.9)
Lau[7]	Canada	Sensitizing mutations only	412	67	68	First-generation	25.0 (23.1-27.5)
			70	62	63	Afatinib	39.0 (25.6-48.8)
Gijtenbeek (this study)	NL	No exclusions	596	65	68	Total	20.2 (17.8-23.2)
						Gefitinib	18.3 (14.7-25.5)
						Erlotinib	21.7 (17.9-24.7)
						Afatinib	20.8 (15.4-24.3)

Abbreviations: CI = Confidence interval; EGFR = Epidermal growth factor receptor; NL = The Netherlands; NS = not significant; TKI = tyrosine kinase inhibitor; USA = United States.

- The now observed differences in outcomes between the different first- and second-generation line TKIs suggests that future EGFR TKI development will have to involve evaluations of the treatment response patterns of distant metastasis and the spectrum of resistance mutations. The now found differences in response remain important when, in the future, multiple third-line EGFR TKIs become available.

Disclosure

H.J.M. Groen reports fees for advisory work from Roche-Genentech, Merck and from BMS, outside the submitted work; and money goes to UMCG. A.J. van der Wekken reports grants and personal fees from Astra Zeneca, grants and personal fees from Boehringer Ingelheim, grants and personal fees from Pfizer, personal fees from Novartis, personal fees from Roche (diagnostics), personal fees from Lilly, outside the submitted work; and money goes to UMCG. W.H. van Geffen reports a grant to the institution from Novartis, for an investigator-initiated trial outside the submitted work. The remaining authors have stated that they have no conflicts of interest.

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