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Effectiveness of erlotinib treatment in advanced KRAS mutation-negative lung adenocarcinoma patients: Results of a multicenter observational cohort study (MOTIVATE)

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ABSTRACT

Objectives: Erlotinib is an epidermal growth factor receptor tyrosine-kinase inhibitor (EGFR-TKI), used for the treatment of non-small cell lung cancer. As the clinical significance of KRAS mutational status has not yet been clearly determined in this setting, our aim was to investigate the efficacy of erlotinib in advanced KRAS mutation-negative lung adenocarcinoma patients.

Materials and methods: MOTIVATE is an open-label, multicenter, observational trial with Tarceva® (erlotinib) monotherapy. Enrolled patients with advanced (stage IIIB/IV) KRAS wild type (WT) lung adenocarcinoma refractory to one or two courses of prior chemotherapy were treated with erlotinib at 150 mg/day. The primary endpoint was progression-free survival (PFS). Secondary endpoints were overall survival (OS) and best tumor response rate (RR).

Results and conclusion: In total, 327 patients were included. Median PFS and OS were 3.3 and 14.4 months, respectively. Three patients (1.2%) had complete response, 51 patients (20.2%) had partial response and 123 patients (48.8%) had SD.

Significantly longer median PFS and OS were observed in Eastern Oncology Cooperative Group Performance Status (ECOG PS) 0-1 patients, as compared to ECOG PS 2-3 patients. The longest median OS (20.5 months) was found in patients with ECOG PS 0-1 who received erlotinib as a second-line therapy. There was no difference in median OS in cohorts stratified to disease stage and smoking status. Female patients had both longer median PFS and OS. Disease control rate was 70.2%.

Our results suggest that erlotinib represents a valid treatment option for patients with KRAS WT lung adenocarcinoma and, moreover, that KRAS mutation analysis could help to identify clinically relevant subgroups of NSCLC patients that may benefit from EGFR-TKI therapy.

1. Background

Although the incidence of lung cancer shows a decreasing trend in the western world, in addition to prostate and breast cancers it remains one of the leading cancer types both among men and women, and is the main cause of cancer related mortality in the US, as well as in Europe [1,2]. Hungary ranks first in the world with respect to lung cancer incidence and mortality among men [3].

In the last decades, the incidence of adenocarcinoma histology increased among non-small cell lung cancer (NSCLC) patients [4].

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In the western world, in patients with lung adenocarcinoma, KRAS mutations are the most common (18–38% of cases), followed by mutations in the epidermal growth factor receptor (EGFR) gene (5–15% of cases) [5–8]. In Hungary, the incidence of KRAS mutation in lung adenocarcinoma is 29.5% (based on the analysis of 6250 patients; unpublished data). Smoking status influences the mutation of these two genes: KRAS mutation is found mainly in smokers, whereas the mutation of EGFR gene is more frequent in non-smokers [6,9].

Erlotinib (OSI 744, Tarceva®, Genentech (Roche), USA) is a potent, orally administered epidermal growth factor receptor tyrosine-kinase inhibitor (EGFR-TKI), which is well tolerated and has been proven to prolong survival, delay symptom progression and improve quality of life versus placebo in patients with previously treated, advanced NSCLC in a large phase III trial (BR.21) [10,11]. Moreover, erlotinib is more effective as a first-line treatment than standard chemotherapy in patients with exon 19 deletions or exon 21 (L858R) substitution mutations of EGFR [12,13]. In addition to any line of treatment of locally advanced, metastatic NSCLC patients harboring EGFR activating mutations, erlotinib is also approved without biomarker selection in the second and third line therapy of NSCLC, and also as a maintenance treatment for patients with stable, locally advanced or metastatic NSCLC after four cycles of platinum-based chemotherapy [14].

EGFR mutation is associated with adenocarcinoma histology, often found in non-smokers and more frequent in females, especially in patients of Asian origin. Thus, patients with such characteristics are likely to respond better to erlotinib [15]. Moreover, the presence of KRAS mutations seems to be mutually exclusive with EGFR mutations, and is associated with the absence of response to EGFR-TKIs [16–18]. It has been confirmed that smokers with adenocarcinoma of the lung are more likely to have KRAS mutation positive tumors compared to non-smokers [6]. Erlotinib treatment is particularly effective in terms of survival and tumor response in patients with the aforementioned clinicopathological characteristics. In Hungary, the drug is approved for KRAS mutation negative (wild-type; WT) lung adenocarcinomas after failure of at least one prior chemotherapy regimen. This observational cohort study was conducted to prospectively collect efficacy data of erlotinib in routine clinical practice, focusing on two potential predictive factors of erlotinib treatment, adenocarcinoma histology and KRAS mutational status.

2. Materials and methods

2.1. Study design

The study ML21623 – MOTIVATE, an open-label, non-randomized, multicenter, non-interventional trial of erlotinib monotherapy – investigated the efficacy of erlotinib in routine clinical practice in Hungary. Study population included patients with advanced (stage IIIB/IV) KRAS mutation-negative lung adenocarcinoma previously treated with one or two lines of standard systemic chemotherapy. The primary endpoint was progression-free survival (PFS), secondary endpoints were overall survival (OS), and best overall tumor response. This publication presents the final efficacy results of the MOTIVATE trial.

2.2. KRAS mutation analysis

Mutations in codons 12 and 13 of exon 2 of the KRAS gene were analyzed as recently described [19]. Briefly, tumor-rich microscopic area on H&E staining had been determined by a pathologist prior to macrodissection from the formalin fixed paraffin-embedded tissue. DNA was extracted using the MasterPure™ DNA Purification Kit (Epicentre Biotechnologies, WI) according to the instructions of the manufacturer. KRAS mutations were screened by a microfluid-based restriction fragment detection system characterized by 5% mutant tumor cell content sensitivity. The sense primer was a mismatch primer, and the PCR product contained the recognition site of BstNI or BglI restriction endonuclease in case of the WT KRAS gene. DNA amplifications were performed with AmpliTaq Gold (Applied Biosystems Inc., CA) and primer pairs as follows: KRAS codon 12: 5′-GAATATAAACTTGTGGTAGTTGGACCT-3′ and 5′-GGTCCTGCACCAGTAATATG-3′ and codon 13: 5′-GAATATAA-ACTTGTGGTAGTTGGACCT-3′ and 5′-GGTCCTGCACCAGTAATATG-3′. The reaction mixture of reagents for samples was prepared, containing 2.5 μl 10× PCR buffer + Mg^{2+}, 200 μM from each dNTP, 1.00 pM/reaction of each primer, 0.8 U of AmpliTaq Gold DNA polymerase per reaction. Both reactions went through 38 cycles of denaturation at 95 °C for 1 min, primer annealing at 55 °C for 1 min and chain elongation at 72 °C for 2 min. The amplified products were digested with 80 U BstNI (New England BioLabs, MA) at codon 12 and 80 U BglI at codon 13. Enzymatic digestions were performed at 60 °C (codon 12) and 37 °C (codon 13) for 4 h in a total volume of 30 μL. The digested PCR products were analyzed by microfluid based Experion gel electrophoresis system (Experion™ DNA 1 K Analysis Kit; Bio-Rad Laboratories, CA). Density ratio of the mutated band to the WT one was calculated and samples containing >5% of the non-WT band were considered mutation positive due to the sensitivity threshold. Base-pair substitutions in mutant samples were verified and determined by sequencing on the ABI 3130 Genetic Analyzer System (Life Technologies, Carlsbad, CA) with the BigDye® Terminator v1.1 Kit.

2.3. Eligibility criteria

Patients above the age of 18 years with histologically or cytologically documented inoperable, locally advanced, recurrent or metastatic (stage IIIB/IV – according to the 6th Edition of the UICC-AJCC TNM Classification) NSCLC were included in the study. Erlotinib therapy was administered according to the Summary of Product Characteristics (SPC) of Tarceva and the present Hungarian reimbursement criteria (i.e. KRAS WT lung adenocarcinoma patients who have received at least one course of standard chemotherapy). Exclusion criteria were also in accordance with the SPC. All patients provided written informed consent, and the protocol was approved by the Scientific and Research Ethics Committee of the Medical Research Council (No.: 882-0/2010-1018EKU) and Ethics and Scientific Committees of participating centers.

2.4. Study treatment

Patients received erlotinib 150 mg/day orally until disease progression or unacceptable toxicity. As this was an observational trial, dose modification of erlotinib and any additional treatment or concomitant medication was at the discretion of the investigators. Response grading (by using CT, MRI, X-ray and US) was evaluated by two independent expert investigators in every two month as per institutional standard of care. The protocol did not require the confirmation of complete or partial response.

2.5. Statistical analysis

Descriptive statistical methods were used for analyzing efficacy data. Kaplan–Meier curves were generated to show PFS and OS. Differences between groups were calculated with Log Rank test. PFS was defined as the time from the start of administration of erlotinib to the first documented progression or death. For patients

Table 1
Baseline demographic and clinical characteristics.

Characteristic		*n* (%)
Total number of patients		327
Age (years)	Median	60.8
Gender	Male	164 (50.2)
	Female	163 (49.8)
Ethnic origin	Caucasian/white	327 (100.0)
ECOG PS	0	118 (36.1)
	1	169 (51.7)
	2	36 (11.0)
	3	4 (1.2)
Stage	Stage IIIb	101 (30.9)
	Stage IV	226 (69.1)
Prior chemotherapy	Erlotinib second-line	214 (65.4)
	Erlotinib third-line	113 (34.6)
Smoking status	Never smoker	104 (31.8)
	Former smoker	128 (39.1)
	Current smoker	95 (29.1)

ECOG = European Cooperative Oncology Group. PS = Performance Status.

where these time points were unavailable, the date of last visit or last contact was the censored time point.

3. Results

3.1. Patient characteristics

From 27 participating centers, 327 patients with KRAS WT lung adenocarcinoma were enrolled in the study. Accrual was performed between February 2008 and December 2010. The data cut-off date was 15 April 2011. Baseline demographic and clinical characteristics are summarized in Table 1. All 327 patients were of Caucasian origin. Of these, 164 (50.2%) were male and 163 (49.8%) were female. Median age at the time of enrollment was 60.8 years. 31.1% and 68.9% of the patients had stage IIIB and IV disease, respectively. Approximately two-third of the patients received erlotinib as second-line, and one-third as third-line therapy.

3.2. Efficacy results

Median PFS was 3.3 months (95% CI 2.93–3.67), and median OS was 14.4 months (95% CI 9.46–19.34). Median PFS and OS were significantly longer in females when compared to males (3.8 [95% CI 2.85–4.75] vs. 3.2 [95% CI 2.99–3.41] months [$p < 0.01$] and 20.5 [95% CI 10.36–30.71] vs. 9.4 months [95% CI 6.29–12.45] [$p = 0.042$], respectively) (Fig. 1a).

Median OS was longer in patients receiving erlotinib second-line versus those who received erlotinib third-line (16.1 months [95% CI 8.93–23.33] vs. 9.3 months [95% CI 7.01–11.53]; $p = 0.631$) (Fig. 1b).

No difference was observed in OS when stratified to disease stage (IIIB vs. IV) or smoking status (Fig. 1c), although in the third-line treated group never-smoker patients lived twice as long, as current smokers (11 vs. 5.5 months), which was a significant difference ($p = 0.039$).

A significant and clinically meaningful correlation was observed between Eastern Oncology Cooperative Group Performance Status (ECOG PS) and survival. This difference in OS, but not in PFS, remained strongly significant when treatment line and ECOG PS were both taken into consideration ($p < 0.001$). The longest median OS (20.5 months [95% CI 12.67–28.39]) was observed in patients with ECOG PS 0-1 receiving erlotinib in second-line (Fig. 1d), and in patients with ECOG PS 0, irrespective of the line of treatment

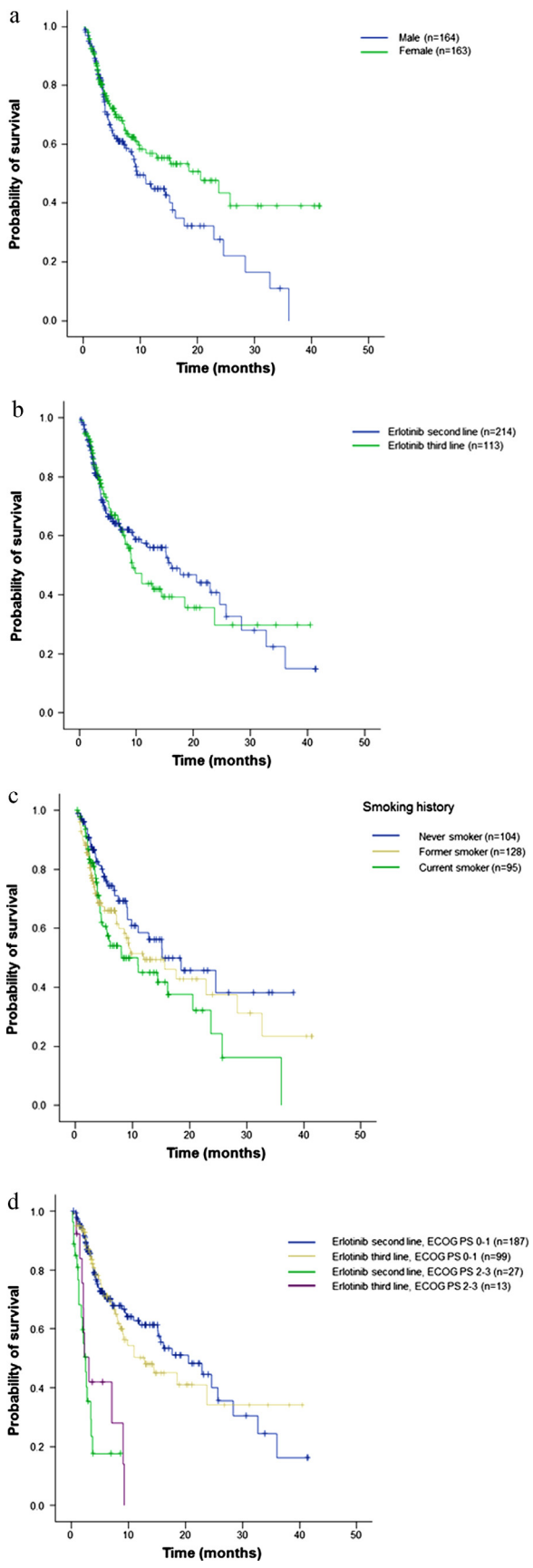

Fig. 1. (a) Overall survival according to gender. (b) Overall survival according to line of treatment. (c) Overall survival according to smoking status. (d) Overall survival according to line of treatment and ECOG PS status.

Table 2
PFS and OS according to different baseline characteristics.

Characteristic		PFS (months (95% CI))	*p* value[a]	OS (months (95% CI))	*p* value[a]
Gender	Male	3.2 (2.99–3.41)	<0.01	9.4 (6.29–12.45)	0.02
	Female	3.8 (2.85–4.75)		20.5 (10.36–30.71)	
Stage	IIIB	3.5 (2.75–4.19)	0.697	15.6 (9.70–21.57)	0.063
	IV	3.2 (2.73–3.74)		11.0 (5.48–16.46)	
Smoking status	Never smoker	3.5 (1.78–5.28)	0.467	15.2 (6.12–24.28)	0.085
	Former smoker	3.2 (2.89–3.58)		11.9 (4.79–19.02)	
	Current smoker	3.3 (2.73–3.87)		10.9 (3.28–18.52)	
ECOG PS	0	4.8 (2.96–6.57)	<0.001	25.7 (16.28–35.12)	<0.001
	1	3.1 (2.79–3.34)		10.9 (5.40–16.40)	
	2	2.1 (0.96–3.18)		2.5 (1.85–3.15)	
	3	1.7 (NA)		1.9 (1.61–2.25)	

[a] Log-rank test.

(median OS: 25.7 months [95% CI 16.83–35.12]). The effect of different baseline characteristics on erlotinib treatment is summarized in Table 2.

Dose modification was necessary for 48 patients, mainly because of skin rash and diarrhea (Table 3). A longer median PFS was detected for those who needed dose modification (8.5 [95% CI 5.44–11.56] vs. 3.1 [95% CI 2.97–3.30] months [$p < 0.001$]).

Best response data were available for 252 patients. Complete response (CR) was achieved in 3 patients (1.2%), partial response (PR) was detected as best response in 51 patients (20.2%), and stable disease (SD) was achieved in 123 patients (48.8%), all together resulting in a disease control rate of 70.2%. Progressive disease (PD) as best tumor response was reported in 75 patients (29.8%).

4. Discussion

Data of two pivotal studies are available so far where erlotinib was compared with placebo in advanced NSCLC patients. In the BR.21 study, erlotinib led to a significantly better response rate, median PFS and OS than placebo in the entire previously treated, unselected NSCLC patient population [10]. In the SATURN study, erlotinib maintenance therapy for non-progressive disease after first-line platinum treatment resulted in significantly longer median PFS for the whole study population, and also for the EGFR mutant subgroup [20].

Analysis of the EGFR WT subgroup of both studies showed that erlotinib is an effective drug in this patient population in terms of median PFS and OS compared to placebo [21]. In contrast, in the ISEL study, gefitinib did not show survival benefit for advanced NSCLC patients but predicted longer median OS for never-smoker and Asian patients. The observation that these attributes are linked with EGFR mutation status [22] suggests that gefitinib is effective in the EGFR mutant subgroup.

The efficacy of erlotinib as second- or third-line treatment in EGFR WT NSCLC patients is still controversial. The TAILOR study showed significantly increased median PFS and a non-significant but clinically meaningful median OS for patients treated with docetaxel in this patient population [23] and the DELTA study also demonstrated a longer median PFS in the docetaxel group, which however did not translate to overall survival benefit [24]. These results indicate that EGFR WT tumors are heterogeneous.

Table 3
Erlotinib dose reduction.

Cause of dose reduction	Patients (%)	Dose reduction (%)
Skin rash	11.0	53.7
Diarrhea	4.3	20.9
Other	2.8	13.4
No data available	2.8	11.9

It is very important to emphasize that EGFR WT NSCLC is heterogeneous and includes KRAS mutant cases, where the efficacy of erlotinib is least expected.

We performed an open-label, non-randomized, multicenter, non-interventional trial of erlotinib monotherapy in patients with advanced KRAS WT lung adenocarcinoma. Our results confirmed the efficacy of erlotinib with a median PFS of 3.3 months, a median OS of 14.4 months and a disease control rate of 70.2% in this study population.

The results of the present study are comparable to those from the HORG trial, which compared pemetrexed with erlotinib in previously treated NSCLC patients [25]. Authors of this study found that patients with KRAS WT tumors treated with erlotinib had a significantly better median OS than the KRAS mutant subgroup (11.9 vs. 3.9 months; $p = .001$). The TITAN study compared erlotinib with chemotherapy (pemetrexed or docetaxel) as second-line treatment of histologically unselected advanced NSCLC patients. No difference was found between the two groups with respect to median OS, neither for the whole population, nor for EGFR WT patients. Nevertheless, the risk of death was lower in the erlotinib group of the KRAS WT population ($p = 0.041$) [26]. The objective tumor response rate of the erlotinib-arm in the TAILOR study was 3% [23]. This is in contrast with the response rate of 21.4% in our cohort. Disease control rates were 26% and 70.2% in the TAILOR and in our study, respectively. These differences might be explained by the different patient populations (i.e. the TAILOR study involved KRAS mutant cases with the exclusion of EGFR mutant ones, while our study enrolled patients with KRAS WT tumors thus increasing the number of cases with EGFR mutant tumors).

Earlier studies indicated that KRAS mutant NSCLC patients fail to benefit either from adjuvant chemotherapy or from EGFR inhibitors [7,16,27–29]. Lack of EGFR mutation status of the KRAS WT patients represents a major limitation of our study (i.e. the presented cohort selected for WT KRAS is composed of EGFR mutant and EGFR WT patients, and thus it is enriched to some extent for EGFR mutant cases). Of note, however, when this study was initiated, EGFR status was not regarded as a predictor of EGFR inhibitor efficacy and our central aim was to confirm or rule out if KRAS mutational status in itself (i.e. without the knowledge of patients' EGFR status) has a predictive role for the second or third-line erlotinib therapy of NSCLC. Importantly, although the role of KRAS mutational analysis in NSCLC treatment is still debated [30–32], our data suggest a predictive role of KRAS status for NSCLC patients treated with erlotinib and, furthermore, are in line with subsequently published NCCN NSCLC guidelines which has been incorporated the proposal that "KRAS mutations are associated with intrinsic TKI resistance, and

KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy" [18].

As KRAS mutation is found mainly in smokers [6,33], the negative prognostic value of KRAS mutation may be related to the poor performance status associated with smoking [34]. In our study, no significant difference was observed in survival when stratified according to smoking status in the entire patient population. The lower incidence of KRAS mutation in non-smokers and the low number of current smokers in the present study may explain this effect.

In conclusion, the clinical value of KRAS mutation to predict therapeutic response to EGFR-TKI treatment in NSCLC remains ambiguous and thus EGFR mutational status analysis is currently the preferred test in this setting [35–38]. In part because of ethical objections our study did not involve a cohort of patients with KRAS-mutated NSCLCs. However, the relatively high median PFS and OS data observed in our study do not only suggest that second or third-line erlotinib therapy confers significant benefit to patients with advanced stage KRAS WT lung adenocarcinoma but our findings also support the well-known but still ambiguous concept [35–38] that KRAS mutation analysis might predict treatment non-response to EGFR TKI therapy in NSCLC.

Conflict of interest statement

Authors declare no conflict of interest. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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