doi:10.4149/neo_2013_004

Skin rash as useful marker of erlotinib efficacy in NSCLC and its impact on clinical practice

O. FIALA[1,*], M. PESEK[2], J. FINEK[1], J. KREJCI[3], J. RICAR[4], Z. BORTLICEK[5], L. BENESOVA[6], M. MINARIK[6]

[1]Department of Oncology and Radiotherapy, University Hospital in Pilsen; [2]Department of Tuberculosis and Respiratory Diseases, University Hospital in Pilsen; [3]Department of Pneumology and Thoracic Surgery, University Hospital in Prague-Bulovka; [4]Department of Dermatovenerology, University Hospital in Pilsen; [5]Institut of Biostatistics and Analyses, Masaryk University, Brno; [6]Center for Applied Genomics of Solid Tumors (CEGES), Genomac Research Institute, Prague

**Correspondence: fiala.o@centrum.cz*

Received March 29, 2012 / Accepted June 6, 2012

Erlotinib is an epidermal growth factor receptor tyrosine kinase inhibitor used in treatment of advanced NSCLC. Patients harboring EGFR or KRAS mutations represent minority of all patients in caucasian population and there is no available predictor for a predominant group of patients harboring the wild-type EGFR and wild-type KRAS genes. Skin rash is the most frequent manifestation of cutaneous toxicity of erlotinib. Rash is associated with a good therapeutic response. We aimed at the evaluation of rash as a predictor of therapeutic effect of erlotinib in patients harboring the wild-type EGFR and KRAS wild-type genes and to assess its possible usage in a clinical practice.

Totally 184 patients with advanced stage NSCLC (IIIB, IV) harboring the wild-type EGFR and wild-type KRAS genes were analysed. Comparison of ORR, PFS and OS according to the occurrence of rash was performed. In order to assess the impact of rash in clinical practice it was conducted landmark analysis of the group of patients whose rash was observed during first month of treatment (n=124). Patients in whom progression was observed during the first month of treatment were excluded from the landmark analysis. The comparison of ORR was performed using Fisher's exact test, visualization of survival was performed using Kaplan-Meier survival curves and the differences in survival were tested using the log-rank test.

Median PFS in patients who were observed with rash during the treatment was 3.0 vs. 1.2 months in patients with no rash ($p<0.001$), median of OS in patients who were observed with rash during the treatment was 13.9 vs. 5.8 months in patients with no rash ($p<0.001$). ORR in patients who were observed with rash during the treatment was 17.4% vs. 3.3% in patients with no rash ($p=0.001$). Median of PFS after 1 month of treatment in patients who were observed with rash during the first month was 2.9 vs. 1.1 months in patients with no rash ($p=0.027$). Median of OS after 1 month of treatment in patients who were observed with rash during the first month was 13.8 vs. 9.9 months in patients with no rash ($p=0.082$).

Rash is strongly associated with better survival and ORR in patients harboring wild-type EGFR and wild-type KRAS genes. Occurrence of rash during the first month of treatment is a useful predictor of better effect of erlotinib after one month of treatment. Patients who were not observed with rash during the first month of treatment are in high risk of progression. Optimization of the treatment of these patients can contribute restaging after two months of treatment, assessment of plasma levels of erlotinib and eventually attempt to dose escalation.

Key words: erlotinib, NSCLC, rash, targeted traetment, skin toxicity

Lung cancer is a principal cause of cancer-related deaths worldwide and its incidence has been still increasing. Non-small cell lung cancer (NSCLC) is the most common histological type of lung cancer constituting more than 80% of all lung carcinomas. Molecular targeted therapy based on tyrozine kinase inhibitors (TKI), directed at epidermal growth factor receptor (EGFR) is one of the most effective tools in management of advanced NSCLC. Erlotinib is a low molecular weight tyrosine kinase inhibitor blocking the activation of EGFR cascade. In clinical practice today erlotinib

is commonly used for treatment of advanced stage NSCLC (stage IIIB and IV).

Searching for predictors of EGFR-TKI therapy achieved good results especially in the field of molecular genetics. A presence of activating mutations in EGFR gene is currently the best predictor of therapeutic effect of EGFR-TKI [1-5]. Frequency of EGFR mutations is 5–20%, predominantly in asians, women with adenocarcinoma histology and never smokers [5-7]. KRAS mutations represent another molecular marker frequently related to effectiveness of EGFR-TKI therapy. Mutated KRAS gene has indeed been widely reported as a negative predictor for EGFR-TKI therapy as well as a negative prognostic factor in NSCLC [8-11]. Frequency of KRAS mutations is 15-25%, predominantly in caucasians and smokers [12,13]. Patients harboring EGFR or KRAS mutations represent a minority of all patients with advanced NSCLC. There is no available predictive marker suitable for usage in clinical practice for the predominant group of patients harboring the wild-type EGFR and wild-type KRAS genes.

Skin rash is the most common manifestation of cutaneous toxicity of erlotinib. It occurs approximately in two-thirds of treated patients. [14-17]. Retrospective analyses of wide variety of studies have suggested that skin toxicity correlates with survival and therapeutic response. In the BR.21 placebo-controlled phase III trial of erlotinib in previously treated patients with advanced NSCLC, the median survival for erlotinib-treated patients who did not experience skin toxicity was 3 months compared with 7 and 11 months for those with grade 1 or 2/3 skin toxicity, respectively [18]. Similar relationships have been observed in the clinical trials of erlotinib in NSCLC [19-24].

We focused on the evaluation of rash as a marker of treatment efficacy in genetically determined group of patients harboring the wild-type EGFR and wild-type KRAS genes and subsequently to evaluate its possible usage in a clinical practice.

Patients and methods

Patients and statistical methodology. We analysed data of patients with cytologically or histologically confirmed advanced stage (IIIB, IV) NSCLC enrolled in the Tarceva clinical registry. Patients were treated at the Department of Tuberculosis and Respiratory Diseases at the University Hospital in Pilsen. The treatment with erlotinib was prospectively monitored, the efficacy and the incidence and type of adverse reaction were continuously assessed at specific time points. The total number of genetically tested patients treated with erlotinib in the 1.-4. line was 255. 71 patients harboring mutation of EGFR or KRAS gene were excluded from the analysis. Totally 184 patients harboring the wild-type EGFR and wild-type KRAS genes were closely analysed.

The comparison of overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) between two groups of patients was performed. The first group represented patients who were observed with rash (n=92). The second group represented patients in whom no rash was observed (n=92). The patients´ characteristics are summarized in the Table 1.

In order to assess the impact of rash on a clinical practice it was conducted a landmark analysis at one month after beginning of the treatment. Patients in whom progression was observed within 1 month after beginning of the treatment were excluded from the ladmark analysis. According to these criteria a comparison of PFS and OS were performed between groups of patients with rash observed within the first month (n=65) and without rash (n=59). The patients´ characteristics are summarized in the table 2.

Treatment response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST). Comparison of ORR (complete response + partial response) was performed using the Fisher‘s exact test. The visualization of OS and PFS as well as the estimation of survival probabilities was performed using Kaplan-Meier survival curves; all point estimates were accompanied with 95% confidence intervals. The differences in survival were tested using the log-rank test. As a level of statistical significance, α=0.05 was used. Patients´ groups were compared according to the age using Mann-Whitney test. The Fisher's exact test was used for comparison according to sex, smoking history, histological type, stage, ECOG PS and line of the treatment. As a level of statistical significance, α=0.05 was used.

Mutation analysis of EGFR and KRAS genes. The tumor specimens acquired during an initial bronschoscopy examination were evaluated by a senior cytologist using a regular giemsa staining. In a few cases a tumor biopsy was processed into formalin-fixed paraffin embedded (FFPE) histology sections. The cytology slides or, eventually, the FFPE sections, were submitted for molecular genetic test being included detection of somatic mutations in EGFR and KRAS genes. If it was necessary, tumor cells were carefully selected and removed from the samples by laser microdissection using a P.A.L.M. microlaser instrument [Carl Zeiss MicroImaging GmbH, Germany]. The microdissected cells were collected directly into the PCR buffer and processed without a special DNA extraction step. In all other cases the DNA was extracted from tissue cells by a standard spin column procedure using JetQuick Tissue DNA Issolation Kit [GENOMED GmbH, Loehne, Germany]. The mutations in exons 19 and 21 of EGFR gene and exon 1 of KRAS gene were examined through Genoscan KRAS and Genoscan EGFR kits [Genomac International, Prague, Czech Republic] utilizing a denaturing capillary electrophoresis (DCE) technique on ABI PRISM 3100 16-capillary genetic analyzer. Detected mutations were identified by regular DNA sequencing using a BigDye v 3.0 chemistry (Applied Biosystems, Foster City, CA). In rare cases, where the overall fraction of mutated DNA was below the 20% minimum required for DNA sequencing, mutation was identified indirectly after forming only a homoduplex fragment with a given known mutation reference standard.

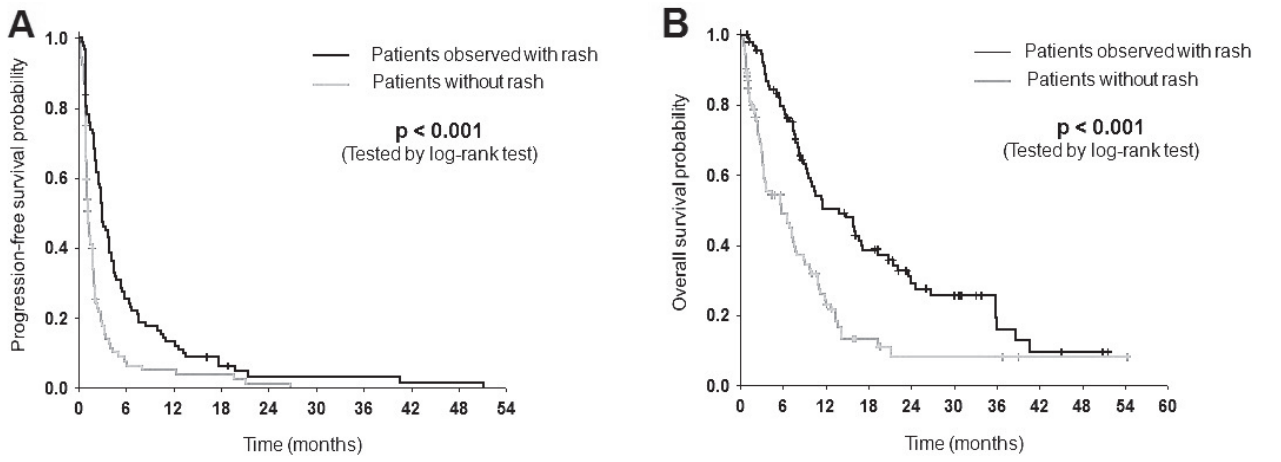

Figure 1. Comparison of PFS (A) and OS (B) between patients who observed with rash and patients without rash.

Assessment of erlotinib toxicity. In the study group we observed papulopustular (acneiform) eruption, xerosis, asteatotic eczema, fissures, hyperpigmentations, hair and nail changes, teleangiectasias and rarely mucosal changes. Cutaneous toxicity was classified in agreement with the National Cancer Institute Common Terminology Criteria for Adverse

Table 1. Basic clinical characteristics of patients

	Patients observed with rash (n = 92)		**Patients without rash** (n = 92)			
Sex					Fisher's exact test	**p = 0.223**
Female	30	32.60%	39	42.40%		
Male	62	67.40%	53	57.60%		
Age					Mann-Whitney test	**p = 0.464**
Median	63		62			
Average	64		63			
Smoking status					Fisher's exact test	**p = 0.493**
Non smoker	25	27.20%	20	21.70%		
Former smoker	34	37.00%	22	23.90%		
Smoker	33	35.90%	50	54.30%		
Histological type					Fisher's exact test	**p = 0.069**
Adenocarcinoma	44	47.80%	58	63.00%		
Squamous cell carcinoma	40	43.50%	31	33.70%		
Dediferentiated carcinoma	8	8.70%	3	3.30%		
Line of treatment					Fisher's exact test	**p = 0.146**
1. line	10	10.90%	13	14.10%		
2. line	39	42.40%	30	32.60%		
3. line	40	43.50%	49	53.30%		
4. line	3	3.30%	0	0.00%		
ECOG PS					Fisher's exact test	**p = 0.782**
0	1	1.10%	1	1.10%		
1	56	56.00%	48	52.20%		
2	32	34.80%	38	41.30%		
3	2	2.20%	4	4.30%		
4	1	1.10%	1	1.10%		
Stage					Fisher's exact test	**p = 0.363**
IIIB	22	23.90%	16	17.40%		
IV	70	76.10%	76	82.60%		

Events version 3.0 (NCI-CTCAE v3.0) up to the more recent version 4.03 (NCI-CTCAE v4.03) [25].

Results

The median value of PFS in patients who were observed with rash (n=92) was 3.0 vs. 1.2 months in patients with no rash (n=92) as shown in Figure 1A, the difference proved high statistically significant (p<0.001). The median value of OS in patients who were observed with rash (n=92) was 13.9 vs. 5.8 months in patients with no rash (n=92) as shown in Figure 1B, the difference proved high statistically significant (p<0.001). In patients who were observed with rash 2 complete responses (CR), 14 partial responses (PR), 48 stable diseases (SD), 23 progressive diseases (PD) were achieved vs. 0 CR, 3PR, 29 SD, 53 PD in patients with no rash as shown in Figure 2. The difference in ORR (CR+PR) proved high statistically significant (p=0.001). There were not statistically significant differences in age (p=0.464), sex (p=0.223), smoking history (p=0.493), histological type (p=0.069), stage (p=0.363), ECOG PS (p=0.782) and line of the treatment (p=0.146) between compared groups (Tab.1).

Landmark analysis at 1 month after beginning of the treatment. The median value of the PFS after 1 month of the treatment in patients who were observed with rash during the first month (n=65) was 2.9 vs. 1.1 months in patients with no rash (n=59) as shown in Figure 3A, the difference proved statistically significant (p=0.027). The median value of OS after 1 month of the treatment in patients who were observed with rash during the first month (n=65) was 13.8 vs. 9.9 months in patients with no rash during the first month (n=59) as shown in Figure 3B, the difference did not prove statistically significant (p=0.082). There was no statistically significant difference in age (p=0.834), sex (p=0.063), smoking history (p=0.828), histological type (p=0.377), stage (p=0.669), ECOG PS (p=0.317) and line of the treatment (p=0.627) between compared groups (Tab.2).

Discussion

Skin rash of any grade was observed in 50% of patients harboring the wild-type EGFR and wild-type KRAS genes treated with erlotinib. Occurrence of rash within the treatment was strongly associated with longer PFS (3.0 vs. 1.2 months, p<0.001, n=184), longer OS (13.9 vs. 5.8 months,

Table 2. Basic clinical characteristics of patients enrolled in landmark analysis at one month after beginning of the treatment.

	Patients observed with rash during 1. month (n = 65)		**Patients without rash during 1. month** (n = 59)			
Sex					Fisher's exact test	**p = 0.063**
Female	19	29.20%	26	44.10%		
Male	46	70.80%	33	55.90%		
Age					Mann-Whitney test	**p = 0.834**
Median	63		62			
Average	63		63			
Smoking status					Fisher's exact test	**p = 0.828**
Non smoker	13	20.00%	13	22.00%		
Former smoker	25	38.50%	16	27.10%		
Smoker	27	41.50%	30	50.80%		
Histological type					Fisher's exact test	**p = 0.377**
Adenocarcinoma	29	44.60%	34	57.60%		
Squamous cell carcinoma	31	47.70%	22	37.30%		
Dediferentiated carcinoma	5	7.70%	3	5.10%		
Line of treatment					Fisher's exact test	**p = 0.627**
1. line	5	7.70%	8	13.60%		
2. line	26	40.00%	19	32.20%		
3. line	32	49.20%	31	52.50%		
4. line	2	3.10%	1	1.70%		
ECOG PS					Fisher's exact test	**p = 0.317**
0	0	0.00%	2	3.40%		
1	43	66.20%	37	62.70%		
2	21	32.30%	16	27.10%		
3	1	1.50%	3	5.10%		
4	0	0.00%	1	1.70%		
Stage					Fisher's exact test	**p = 0.669**
IIIB	16	24.60%	12	20.30%		
IV	49	75.40%	47	79.70%		

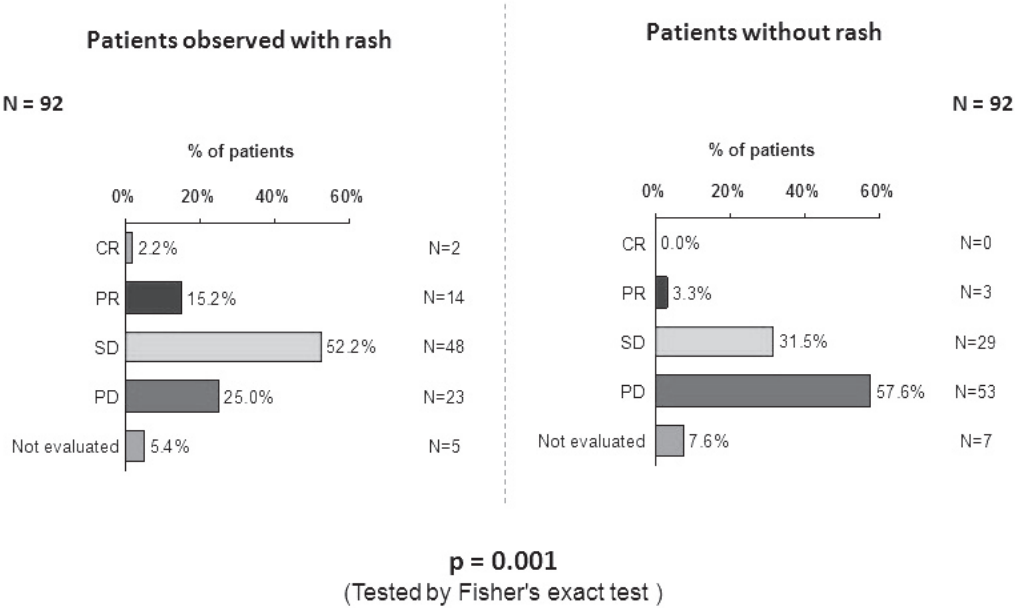

Figure 2. Comparison of ORR between patients who observed with rash and patients without rash.

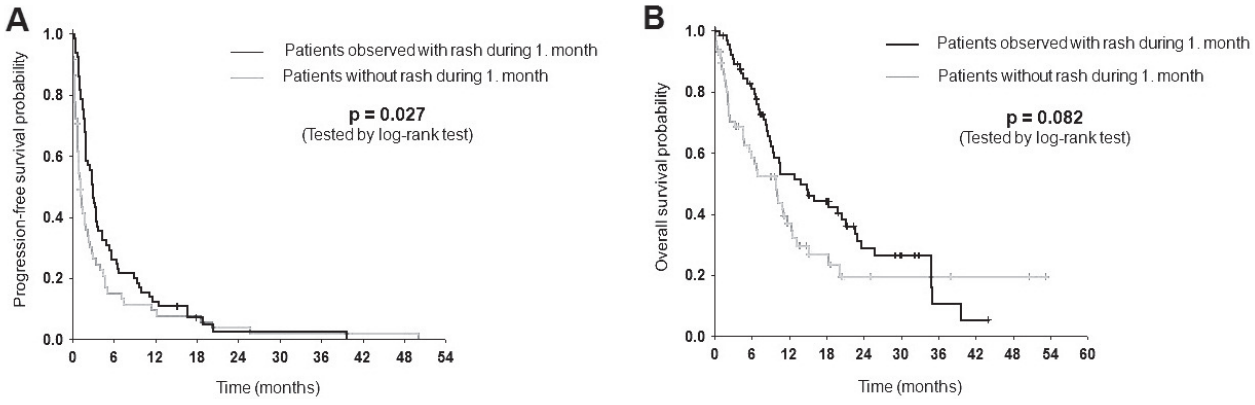

Figure 3. Comparison of PFS (A) and OS (B) after 1 month of the treatment between patients who observed with rash and patients without rash.

p<0.001, n=184) and higher ORR (17.4% vs. 3.3%, p=0.001, n=172). Similar findings were previously reported in the literature [16-21]. These findings indicate that rash is strongly associated with improved anticancer efficacy of erlotinib. This fact may be caused by different pharmacokinetics and higher plasma levels of drug in the subgroup of patients who develop rash.

Results of conducted landmark analysis after one month of the treatment show that occurrence of rash of any grade during the first month predicts significantly longer further PFS (after 1 month of treatment) (2.9 vs. 1.1 months, p=0.027, n=124). The difference in further OS (after 1 month of treatment) did not prove statistically significant, but there was a visible trend (13.8 vs. 9.9 months, p=0.082, n=116). Patients in whom progression was observed within the first month of treatment were excluded from the landmark analysis. When the progression is observed, the treatment is ended immediately. There is no need of marker predicting further treatment efficacy when the progression was observed. Patients harboring wild-type EGFR and wild-type KRAS genes who were not observed with rash of any grade within the first month of erlotinib treatment represent a group with high risk of early progression. Progression within the second month of treatment was observed in 40% patients of this high-risk group. Progression after two months of the treatment was observed mainly using plain chest x-ray hence there is a high probability that if we used CT scan, the number of revealed progressions would be higher. According to these findings, we recommend restaging using CT scan two months

after beginning of the erlotinib treatment for early detection of disease progression in this high-risk patient group. Assessment of plasma levels of erlotinib and dose escalation could be also feasible options for this high-risk patient group. Large clinical trials aiming at improvement of the erlotinib efficacy with higher doses than standard 150 mg are still missing.

Conclusion

Skin rash is strongly associated with better survival and ORR in patients harboring the wild-type EGFR and wild-type KRAS genes. Occurrence of rash within the first month of treatment is a useful marker predicting better further efficacy of erlotinib. Patients harboring the wild-type EGFR and wild-type KRAS genes who were not observed with rash of any grade within the first month of erlotinib treatment are in high risk of progression within the second month of treatment. Optimization of the treatment of these patients can contribute restaging after two months of treatment and assessment of plasma levels of erlotinib. Dose escalation to rash may improve response rates and survival durations.

Acknowledgment: This work was partially supported by the Czech Ministry of Health grant NR9087.

References

[1] LYNCH TJ, BELL DW, SORDELLA R, GURUBHAGAVATULA S, OKIMOTO RA. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib., N Engl J Med. 2004; 350: 2129–39. http://dx.doi.org/10.1056/NEJMoa040938

[2] PAEZ JG, JANNE PA, LEE JC, TRACY S, GREULICH H. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science. 2004; 304: 1497–500. http://dx.doi.org/10.1126/science.1099314

[3] ZHANG Z, STIEGLER AL, BOGGON TJ, KOBAYASHI S, HALMOS B. EGFR-mutated lung cancer: a paradigm of molecular oncology. Oncotarget. 2010; 1: 497–514.

[4] SEQUIST LV, BELL DW, LYNCH TJ, HABER DA. Molecular predictors of response to epidermal growth factor receptor antagonists in non-small-cell lung cancer. J Clin Oncol. 2007; 25: 587–95. http://dx.doi.org/10.1200/JCO.2006.07.3585

[5] RIELY GJ, PAO W, PHAM D, LI AR, RIZVI N et al. Clinical course of patients with non-small cell lung cancer and epidermal growth factor receptor exon 19 and exon 21 mutations treated with gefitinib or erlotinib. Clin Cancer Res. 2006; 12: 839–844. http://dx.doi.org/10.1158/1078-0432.CCR-05-1846

[6] RIELY GJ, POLITI KA, MILLER VA, PAO W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. Clin Cancer Res. 2006; 12: 7232–41. http://dx.doi.org/10.1158/1078-0432.CCR-06-0658

[7] SHIGEMATSU H, LIN L, TAKAHASHI T, NOMURA M, SUZUKI M et al. Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst. 2005; 97: 339–346. http://dx.doi.org/10.1093/jnci/dji055

[8] MARCHETTI A, MILELLA M, FELICIONI L, CAPPUZZO F, IRTELLI L et al. Clinical implications of KRAS mutations in lung cancer patients treated with tyrosine kinase inhibitors: an important role for mutations in minor clones. Neoplasia. 2009; 11: 1084–92

[9] EBERHARD DA, JOHNSON BE, AMLER LC, GODDARD AD, HELDENS SL et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol. 2005; 23: 5900–9. http://dx.doi.org/10.1200/JCO.2005.02.857

[10] BONANNO L, SCHIAVON M, NARDO G, BERTORELLE R, BONALDI L et al. Prognostic and predictive implications of EGFR mutations, EGFR copy number and KRAS mutations in advanced stage lung adenocarcinoma. Anticancer Res. 2010; 30: 5121–8

[11] LIU HP, ISAAC WU HD, CHANG JW, WU YC, YANG HY et al. Prognostic implications of epidermal growth factor receptor and KRAS gene mutations and epidermal growth factor receptor gene copy numbers in patients with surgically resectable non-small cell lung cancer in Taiwan. J Thorac Oncol. 2010; 5: 1175–84. http://dx.doi.org/10.1097/JTO.0b013e3181e2f4d6

[12] SUDA K, TOMIZAVA K, MITSUDOMI T. Biological and clinical significance of KRAS mutations in lung cancer: an oncogenic driver that contrasts with EGFR mutation. Cancer Metastasis Rev. 2010; 29: 49–60. http://dx.doi.org/10.1007/s10555-010-9209-4

[13] RODENHUIS S, VAN DE WETERING ML, MOOI WJ, EVERS SG, VAN ZANDWIJK N et al. Mutational activation of the K-RAS oncogene: a possible pathogenetic factor in adenocarcinoma af the lung. N Engl J Med. 1987; 317: 929–935. http://dx.doi.org/10.1056/NEJM198710083171504

[14] SEGAERT S, CHIRITESCU G, LEMMENS L, DUMON K, VAN CUTSEM E et al. Skin toxicities of targeted therapies. Eur J Cancer. 2009, 45 (Suppl. 1): 295–308. http://dx.doi.org/10.1016/S0959-8049(09)70044-9

[15] HEIDARY NH, NAIK H, BURGIN S. Chemotherapeutic agents and the skin: An update. J Am Acad Dermatol. 2008; 58: 545–563. http://dx.doi.org/10.1016/j.jaad.2008.01.001

[16] HU JC, SADEGHI P, PINTER-BROWN LC, YASHAR S, CHIU MW. Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. J Am Acad Dermatol. 2007; 56: 317–26. http://dx.doi.org/10.1016/j.jaad.2006.09.005

[17] DUVIC M. EGFR inhibitor-associated acneiform folliculitis: assessment and management. Am J Clin Dermatol. 2008; ; 9: 285–94. http://dx.doi.org/10.2165/00128071-200809050-00002

[18] WACKER B, NAGRANI T, WEINBERG J, WITT K, CLARK G et al. Correlation between development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III

studies. Clin Cancer Res. 2007; 13: 3913–21. http://dx.doi.org/10.1158/1078-0432.CCR-06-2610

[19] HEIGENER DF, WU YL, VAN ZANDWIJK N, MALI P, HORWOOD K et al. Second-line erlotinib in patients with advanced non-small-cell lung cancer: Subgroup analyses from the TRUST study. Lung Cancer. 2011; 74: 274–9. http://dx.doi.org/10.1016/j.lungcan.2011.02.017

[20] RECK M, VAN ZANDWIJK N, GRIDELLI C, BALIKO Z, RISCHIN D et al. Erlotinib in advanced non-small cell lung cancer: efficacy and safety findings of the global phase IV Tarceva Lung Cancer Survival Treatment study. J Thorac Oncol. 2010; 5: 1616–22. http://dx.doi.org/10.1097/JTO.0b013e3181f1c7b0

[21] GUTTMAN-YASSKY E, MITA A, DE JONGE M, MATTHEWS L, MCCARTHY S et al. Characterisation of the cutaneous pathology in non-small cell lung cancer (NSCLC) patients treated with the EGFR tyrosine kinase inhibitor erlotinib. Eur J Cancer. 2010; 46: 2010–9. http://dx.doi.org/10.1016/j.ejca.2010.04.028

[22] FAEHLING M, ECKERT R, KUOM S, KAMP T, STOIBER KM et al. Benefit of erlotinib in patients with non-small-cell lung cancer is related to smoking status, gender, skin rash and radiological response but not to histology and treatment line. Oncology. 2010; 78: 249–58. http://dx.doi.org/10.1159/000315731

[23] PEREZ-SOLER R. Rash as a surrogate marker for efficacy of epidermal growth factor receptor inhibitors in lung cancer. Clin Lung Cancer. 2006; 8 Suppl 1: S7–14. http://dx.doi.org/10.3816/CLC.2006.s.008

[24] HERBST RS, PRAGER D, HERMANN R, FEHRENBACHER L, JOHNSON BE et al. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol. 2005; 23: 5892–9. http://dx.doi.org/10.1200/JCO.2005.02.840

[25] National Cancer Institute: Common Terminology Criteria for Adverse Events (CTCAE) Version 4.02, http://www.cancer.gov/