Prognostic Impact of Central Nervous System Metastases After Acquired Resistance to EGFR-TKI: Poorer Prognosis Associated with T790M-negative Status and Leptomeningeal Metastases

AKITO HATA[1], NOBUYUKI KATAKAMI[1], HIROSHIGE YOSHIOKA[2], JUMPEI TAKESHITA[1], KOSUKE TANAKA[1], KATSUHIRO MASAGO[1], SHIRO FUJITA[1], REIKO KAJI[1], YUKIHIRO IMAI[1], KAZUYA MONDEN[3], TAKESHI MATSUMOTO[3], KAZUMA NAGATA[3], KYOKO OTSUKA[3], RYO TACHIKAWA[3], KEISUKE TOMII[3], KEI KUNIMASA[2], MASAHIRO IWASAKU[2], AKIHIRO NISHIYAMA[2], TADASHI ISHIDA[2] and YOSHIHIRO NISHIMURA[4]

[1]*Division of Integrated Oncology, Institute of Biomedical Research and Innovation, Kobe, Japan;*
[2]*Department of Respiratory Medicine, Kurashiki Central Hospital, Kurashiki, Japan;*
[3]*Department of Respiratory Medicine, Kobe City Medical Center, General Hospital, Kobe, Japan;*
[4]*Department of Respiratory Medicine, Kobe University School of Medicine, Kobe, Japan*

Abstract. *Aim: The aim of the present study was to investigate the prognostic impact of central nervous system metastases (CNS) after acquired resistance to epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) in EGFR-mutant non-small cell lung cancer (NSCLC). Patients and Methods: We defined CNS-collapse as death due to uncontrolled and progressive CNS metastases. Post-progression survival (PPS) after initial TKI failure and T790M status were retrospectively compared in 92 patients with or without CNS collapse. Results: The median PPS in 32 patients with CNS-collapse (16.7 months) was significantly shorter than that of 60 without (26.8 months) (p=0.0002). T790M was detected in four (12%) out of the 32 CNS-collapse patients and in 26 (43%) out of 60 without (p=0.0026). Median PPS in 39 patients with leptomeningeal metastases (LM) (11.4 months) was significantly shorter versus 53 without (26.8 months) (p=0.0006). The median PPS was 25.1 months in 40 patients with brain metastases and 11.2 months in 52 without (p=0.0387). T790M was detected in 4/5 resected brain tumors (80%) and in 1/26 cerebrospinal fluid (CSF) samples (4%) (p=0.0008). Conclusion: CNS-collapse represented poorer prognosis, which was associated with T790M-negative status and LM. Controlling CNS metastases, especially LM, is important to achieve longer survival.*

Correspondence to: Dr. Akito Hata, Division of Integrated Oncology, Institute of Biomedical Research and Innovation, 2-2, Minatojima-minamimachi, Chuo-ku, Kobe, 650-0047, Japan. Tel: +81 783045200, Fax: +81 783021708, e-mail: a-hata@fbri.org

Key Words: Central nervous system, epidermal growth factor receptor-tyrosine kinase inhibitor, acquired resistance, T790M, leptomeningeal metastases, brain metastases.

Lung cancer is the leading cause of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancers and the majority are already unresectable and metastatic upon their initial diagnosis. Cytotoxic chemotherapies, such as platinum-based regimens, were once the primary therapeutic option for metastatic NSCLC but their advancement has reached a plateau. Molecular-targeted therapies have been developed recently and they have provided a remarkable benefit to patients harboring specific genetic alterations. Somatic mutations in the epidermal growth factor receptor (*EGFR*) gene have been identified in patients with radiographic responses to EGFR-tyrosine kinase inhibitors (TKIs) (1, 2). Currently, the efficacy of up-front EGFR-TKIs has been established for patients harboring *EGFR*-sensitive mutations in prospective randomized phase III trials and the median progression-free survivals (PFSs) are approximately 12 months (3-7).

Despite an initial dramatic response, most patients harboring *EGFR* mutations acquire resistance to EGFR-TKIs. Approximately one-third of the patients appear to develop central nervous system (CNS) metastases, such as brain metastases (BM) and leptomeningeal metastases (LM) after the initial response to an EGFR-TKI (8-10). CNS metastases are generally associated with poor prognosis in NSCLC (11-13) but little is known regarding the prognostic impact of CNS metastases after acquired resistance to EGFR-TKI.

Several acquired resistance mechanisms to EGFR-TKI have been identified (14-19) and the secondary *EGFR* mutation, a point-mutation in exon 20 (T790M), accounts for approximately one-half of the cases of acquired resistance to EGFR-TKI. Recent reports have demonstrated that the presence of T790M predicts a favorable prognosis and indolent progression compared to the absence of T790M after EGFR-TKI failure (20, 21). Notably, T790M is rarely detected in CNS lesions (21). T790M-negative rapid growth cancer cells invading CNS lesions may induce a poorer prognosis (22). We, therefore, consider the low incidence of T790M in CNS lesions to be associated with poorer prognosis after acquired resistance to EGFR-TKI.

The aim of the present study was to investigate the prognostic impact of CNS metastases in *EGFR*-mutant NSCLC patients after acquired resistance to EGFR-TKI. We also examined the association between T790M prevalence and prognosis in patients with CNS metastases, such as BM and LM.

Patients and Methods

Patients. We retrospectively reviewed the cases of 92 *EGFR*-mutant NSCLC patients whose T790M status had been confirmed by re-biopsy after acquired resistance to an EGFR-TKI (gefitinib, erlotinib or afatinib) between May 2008 and October 2013 at our Institutes. Acquired resistance was defined as Jackman *et al*. proposed (23). In their criteria, response or durable stable disease (≥6 months) was confirmed on EGFR-TKI followed by progression while receiving EGFR-TKI. The interval between the initial EGFR-TKI failure and rebiopsy varied among the patients. BM diagnoses were confirmed by magnetic resonance imaging (MRI). LM diagnoses were judged by MRI findings and/or cytology of cerebrospinal fluid (CSF). Informed consent regarding the *EGFR* mutational analysis was obtained from all patients.

EGFR mutational analysis. Re-biopsy was performed for the 92 patients at various sites using a variety of procedures at our institutes. We isolated tumor DNA from these 92 specimens, and we analyzed *EGFR* mutations using the peptide nucleic acid-locked nucleic acid polymerase chain reaction (PCR) clamp method, as described by Nagai *et al*. (24). Twenty patients received rebiopsies at multiple sites and five underwent plural rebiopsies; we adopted the first result of T790M status. Almost all mutation analyses were performed in malignant cell-confirmed specimens but three cytology-negative CSFs revealed *EGFR* mutations. No other acquired resistant molecular mechanisms (*e.g.*, MET) were examined.

Post-progression survival and T790M analysis. To investigate the patients' prognoses after initial EGFR-TKI failure, we examined the periods of post-progression survival (PPS) after initial EGFR-TKI failure and the T790M prevalence in each clinical factor. CNS-collapse was defined as death due to uncontrolled and progressive CNS metastases, which caused performance status (PS) deterioration that prohibited further cytotoxic chemotherapies except for EGFR-TKIs. We compared the PPS and T790M status in the patients with and without CNS-collapse. We also compared the PPS and T790M status in the patients with BM or LM to analyze the prognostic and biological distinction between BM and LM. PPS was herein defined as the period from progressive disease (PD) on initial EGFR-TKI therapy to death.

Statistical analyses. The PD of initial EGFR-TKI therapy was judged by each physician in charge according to clinical progression or objective progression as described by the Response Evaluation Criteria in Solid Tumors, version 1.1. PFS was defined as the length of time from the initiation of the first EGFR-TKI therapy until PD or death. PPS was defined as the date of the PD on initial EGFR-TKI until death. Each patient's characteristics were compared between T790M-positive and -negative patients using the Fisher's exact test. PPS curves were estimated according to the Kaplan-Meier method. PPSs were compared using the log-rank test. A *p*-value less than 0.05 was considered significant. The statistical analyses were performed using JMP 7 (SAS Institute, Inc., Cary, NC, USA).

Results

Patients' characteristics and T790M prevalence. Between May 2008 and October 2013, we retrospectively investigated the prognostic impact of CNS metastases in 92 EGFR-mutant patients whose T790M status had been confirmed after acquired resistance to EGFR-TKI. The patients' characteristics and T790M prevalence are shown in Table I. At the initial mutational analyses, the types of *EGFR* mutation observed before the initial TKI included 45 (49%) deletional mutations in exon 19, 44 (48%) L858R point-mutations in exon 21 and three (3%) point mutations in exon 18 (G719X). Re-biopsy was performed in 31 (34%) CNS lesions (26 CSFs and five brain tumoral tissues), 58 (63%) thoracic lesions (30 lung tissues and 28 pleural effusions) and three (3%) lymph nodes. The median interval between initial TKI progression and re-biopsy was 4.7 months (range=0-60.1 months).

Only two clinical factors were significant for T790M prevalence; the presence of LM and the biopsy site. T790M was identified in five (16%) of 31 CNS specimens and in 25 (41%) of the other 61 lesions (p=0.0191). Six (16%) of the 39 patients with LM harbored T790M, as did 24 (45%) of the 58 patients without LM (p=0.0325). Other characteristics had no significant association with the detection of T790M.

Post-progression survivals and T790M prevalence in patients with and without CNS-collapse. The comparison of the PPS of the patients with and without CNS-collapse is shown in Figure 1. The median PPS with CNS-collapse (n=32) was 16.7 months (95% confidence interval (CI)=9.6–20.1 months) and that without CNS-collapse (n=60) was 26.8 mo (95% CI=14.5-37.3 months) (p=0.0002). Among the 32 patients with CNS-collapse, 31 (97%) out of the 32 patients developed CNS-collapse due to LM and only one (3%) of

Table I. *Patients' characteristics and T790M prevalence.*

Characteristics	Number	T790M (%)	*p*-Value
Age			
≥70	31	13 (42%)	0.2399
<70	61	17 (28%)	
Gender			
Male	31	11 (35%)	0.8144
Female	61	19 (31%)	
Smoking history			
Never	63	21 (33%)	0.8270
Former/Current	29	9 (31%)	
Histology			
Adenocarcinoma	85	30 (35%)	0.0913
Squamous/Large	7	0 (0%)	
Performance Status (ECOG)			
0-1	42	16 (35%)	0.3737
2-4	50	14 (28%)	
Types of *EGFR* mutation			
Exon 18 (G719X)	3	1 (33%)	
Exon 19 (deletion)	45	18 (40%)	0.3200
Exon 21 (L858R)	44	11 (25%)	
Initial TKI			
Gefitinib	73	27 (37%)	0.1021
Erlotinib/Afatinib	18/1	3 (16%)	
Response to Initial TKI			
CR/PR	67	24 (36%)	0.3269
SD	25	6 (24%)	
Line of initial TKI			
First	33	11 (33%)	0.9117
Second or later	59	19 (32%)	
PFS with initial TKI			
≥10 months	51	17 (33%)	0.8686
<10 months	41	13 (32%)	
Interval between TKI failure and rebiopsy			
≥4 months	49	17 (35%)	0.6637
<4 months	43	13 (30%)	
Leptomenigeal metastases			
+	39	6 (15%)	0.0325
–	53	24 (45%)	
Brain metastases			
+	40	12 (30%)	0.6614
–	52	18 (35%)	
Biopsy site			
CNS (Brain/CSF)	5/26	5 (16%)	0.0191
Thoracic/Other	58/3	25 (41%)	

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; CR, complete response; PR, partial response; SD, stable disease; PFS, progression-free survival; CNS, central nervous system; CSF, cerebrospinal fluid.

the 32 cases was due to BM ($p<0.0001$). T790M was detected in four (12%) out of the 32 patients with CNS-collapse and in 26 (43%) of the 60 patients without CNS-collapse ($p=0.0026$). In contrast, CNS-collapse was observed in 28 (45%) of the 62 T790M-negative and four (13%) out of the 30 T790M-positive patients ($p=0.0026$).

Post-progression survival in patients with and without leptomeningeal metastases. The comparison of PPS in patients with and without LM is shown in Figure 2. The median PPS in patients with LM (n=39) was 11.4 months (95% CI, 10.1–23.4 months) and that in the patients without LM (n=53) was 26.8 months (95% CI=16.2-37.3 months) ($p=0.0006$). Six (16%) of the 39 patients with LM harbored T790M and 24 (45%) of the 58 patients without LM harbored T790M ($p=0.0325$). Thirty-one (79%) out of the 39 patients with LM developed CNS-collapse.

Post-progression survival in patients with and without brain metastases. The comparison of PPS in the patients with and without BM is shown in Figure 3. The median PPS in the patients with BM (n=40) was 25.1 months (95% CI=20.4-34.0 months) and that in the patients without BM (n=52) was 11.2 months (95% CI=10.1–23.4 months) ($p=0.0387$). Fifteen (38%) of the 40 patients with BM developed CNS-collapse and the cases of 14 of these 15 (93%) patients were complicated with LM.

T790M status in CSF and brain tumoral tissue. T790M status was examined in five (13%) brain tumoral tissues of the 40 patients with BM and in 26 (67%) CSF samples from 39 patients with LM. T790M was detected in four (80%) out of the five brain tumoral tissues and in one (4%) of the 26 CSF samples ($p=0.0008$).

Discussion

Our data demonstrated that NSCLC patients with CNS-collapse, defined as death due to uncontrolled and progressive CNS metastases after acquired resistance to EGFR-TKI, had poorer prognoses compared to the patients without CNS-collapse (median PPS: 16.7 *vs*. 26.8 months, $p=0.0002$). Approximately one-third of NSCLC patients after initial response to EGFR-TKI appear to develop CNS metastases, such as BM and LM (8-10). CNS metastases are a relatively late complication in the clinical course of patients with advanced NSCLC and its prevalence increases gradually. This increasing prevalence was observed in our cohort of *EGFR*-mutant NSCLC patients; the prevalence of BM and LM was 43% (40/92) and 42% (39/92), respectively. The longer the clinical course, the higher the prevalence of CNS metastases became. Therefore, the control of CNS metastases is extremely important to achieve longer survival after acquired resistance to EGFR-TKI.

The incidence of T790M in patients with CNS-collapse was lower than in those without, whereas T790M-negative patients frequently developed CNS-collapse. We previously demonstrated that the emergence of T790M in CNS is rare compared to other lesions (21). The low incidence of T790M implies the existence of other specific resistance mechanisms

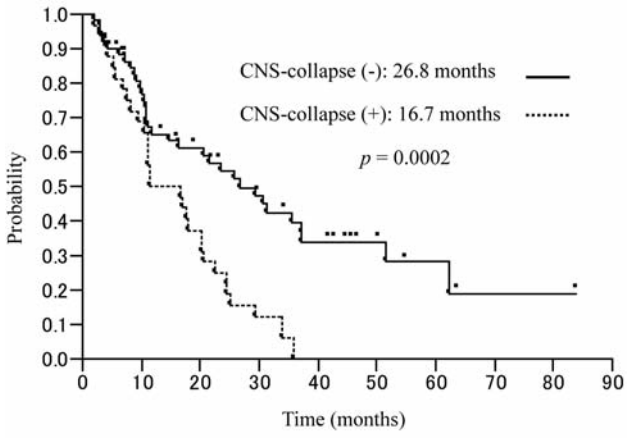

Figure 1. *Post-progression survival of patients with and without CNS-collapse.*

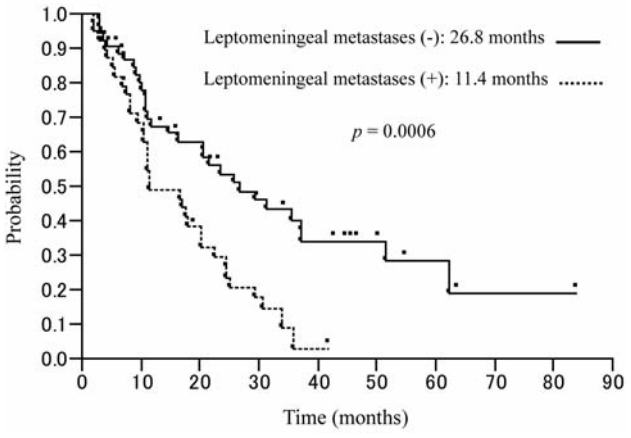

Figure 2. *Post-progression survival of patients with and without leptomeningeal metastases.*

in CNS. This is partially due to poor EGFR-TKI penetration into the CNS, which is called "pharmacokinetic failure." Pre-clinical data demonstrated that T790M-positive cancer cells are mediated by TKI exposure (22). T790M-negative cancer cells have rapid growth potential compared to T790M-positive cancer cells and they frequently metastasize to extrathoracic sites, including the CNS (20, 22). Poor TKI exposure in the CNS may induce a T790M-negative rapid growth cell invasion resulting in poor prognosis. Thus, sufficient drug exposure to the CNS may induce the indolent growth of T790M-positive cancer cells even in the CNS, which may contribute to a better prognosis. In fact, some recent reports demonstrated the efficacy of high-dose EGFR-TKIs in refractory CNS lesions after the failure of standard-dose EGFR-TKIs (25-31).

Our NSCLC patients with LM had a poorer prognosis than those without LM (median PPS: 11.4 *vs.* 26.8 months, p=0.0006). Notably, the PPS curves of the patients with and without LM are similar to the PPS curves of the patients with or without CNS-collapse. Out of the 32 patients with CNS-collapse, 31 (97%) developed CNS-collapse due to LM and only one (3%) developed CNS-collapse due to BM. In contrast, approximately 80% (31/39) of patients with LM developed CNS-collapse. Although the patients with BM had a better prognosis than those without, 15 (38%) of the 40 patients with BM developed CNS-collapse and the cases of 14 of these 15 (93%) patients were complicated with LM. These findings suggest that most patients with LM finally progress to CNS-collapse indicating a relative difficulty to achieve long survival. Even if the patients had only BM without LM in their early clinical courses, complication with LM induces a poor prognosis. We need to explore more effective therapeutic strategies for refractory LM, including high-dose EGFR-TKI, to obtain better prognoses of patients after acquired resistance to EGFR-TKI.

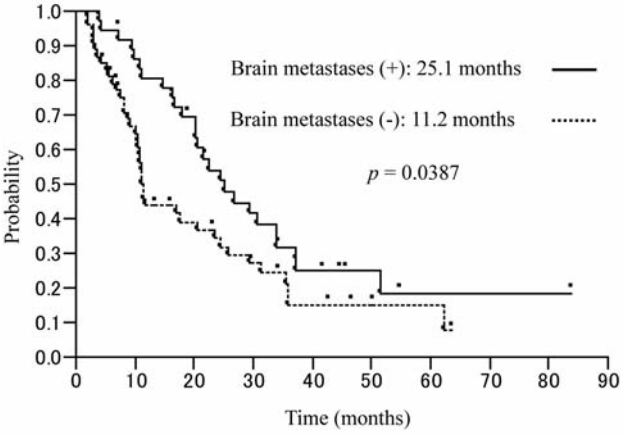

Figure 3. *Post-progression survival of patients with and without brain metastases.*

Interestingly, in our cohort, after acquired resistance to EGFR-TKI, the patients with BM had a better prognosis than those without BM, although BM is generally a poor prognostic factor in patients with NSCLC (11-13). We hypothesize two probable causes. First, BM is treatable in the majority of cases by frequent follow-up with MRI. In our Institutes, MRI is routinely performed every 3-4 months in patients with BM after acquired resistance to EGFR-TKI. Close follow-up using MRI enables the early detection of BM within the stereotactic radiation therapy (SRS) indication window. Early intervention with SRS may be useful to maintain the patient's neurological functions and EGFR-TKI

administration. In disseminated or multiple metastases without SRS indication, whole-brain radiation therapy (WBRT) can be applied. Moreover, some investigators recently reported the efficacy of local therapies with continued EGFR-TKI (32, 33). In patients with a symptomatic solitary metastasis, neurosurgery can be performed. BM in various situations is, thus, treatable in accordance with optimal procedures. Second, BM in patients with *EGFR*-mutant NSCLC may have an indolent nature after acquired resistance to EGFR-TKI. In our cohort, T790M status was examined in five (13%) brain tumoral tissues of 40 patients with BM and T790M was detected in four (80%) of these five tissues. This result suggests that EGFR-TKI exposure is sufficient in cerebral parenchyma, in contrast to CSF. Sufficient exposure of EGFR-TKI can mediate T790M-positive indolent-growing cancer cells in brain metastases. Conversely, T790M-negative rapid-growing cancer cells invade the medullary space due to the insufficient exposure to EGFR-TKI. Notably, we observed an early drop in the PPS curve of the group of patients without BM, which included many patients with LM. These patients with LM had extremely poor prognoses and rarely harbored T790M. We speculate that T790M-negative cancer cells tend to invade the medullary space and induce LM, is was related to poorer prognoses. T790M-positive cancer cells in BM may have a fundamentally indolent nature after acquired resistance to EGFR-TKI.

Our study includes several limitations. First, our cohort is relatively small in size and the data are retrospective. The intervals for the re-staging imaging were highly variable and this represents a bias for PFS assessment of initial TKI. Second, our cohort was limited to patients who had a targetable lesion to undergo rebiopsy. Cases without targetable lesions were not included, which would probably have a relatively small tumor burden and, thus, would have a better prognosis than those with targetable lesions. Third, the presence or absence of CNS-collapse in some patients was difficult to be distinguished if the patients simultaneously had uncontrolled and progressive CNS metastases and systemic disease deterioration. We, thus, had to judge which parameter was more influential in this respect, CNS metastases or systemic progression for PS deterioration.

In conclusion, CNS-collapse represented poorer prognosis, which was associated with T790M-negative status and LM. The patients with LM had a significantly poorer prognosis than those without LM. Conversely, the patients with BM had a better prognosis than those without. In available samples after acquired resistance to EGFR-TKI, T790M was frequently detected in brain tumoral tissue but rarely in CSF. BM and LM appear to have distinct clinical courses and tumor biologies. Since most of the patients with CNS-collapse were due to LM, more effective treatments for refractory LM are required. Future studies are warranted to develop better therapeutic strategies for CNS metastases after acquired resistance to EGFR-TKI.

Funding Sources

No specific funding was disclosed.

Conflicts of Interest

The Authors have declared no conflicts of interest.

Acknowledgements

The Authors would like to thank Mr. David Martin for his writing support.

References

1 Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J and Haber DA: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med *350*: 2129-2139, 2004.

2 Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, Naoki K, Sasaki H, Fujii Y, Eck MJ, Sellers WR, Johnson BE and Meyerson M: EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science *304*: 1497-1500, 2004.

3 Mok TS, Wu YL, Thongprasert S, Yang CH, Chu DT, Saijo N, Sunpaweravong P, Han B, Margono B, Ichinose Y, Nishiwaki Y, Ohe Y, Yang JJ, Chewaskulyong B, Jiang H, Duffield EL, Watkins CL, Armour AA and Fukuoka M: Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med *361*: 947-957, 2009.

4 Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, Seto T, Satouchi M, Tada H, Hirashima T, Asami K, Katakami N, Takada M, Yoshioka H, Shibata K, Kudoh S, Shimizu E, Saito H, Toyooka S, Nakagawa K and Fukuoka M; West Japan Oncology Group: Gefitinib *versus* cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol *11*: 121-128, 2010.

5 Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, Gemma A, Harada M, Yoshizawa H, Kinoshita I, Fujita Y, Okinaga S, Hirano H, Yoshimori K, Harada T, Ogura T, Ando M, Miyazawa H, Tanaka T, Saijo Y, Hagiwara K, Morita S and Nukiwa T; North-East Japan Study Group: Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med *362*: 2380-2388, 2010.

6 Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, Zhang S, Wang J, Zhou S, Ren S, Lu S, Zhang L, Hu C, Hu C, Luo Y, Chen L, Ye M, Huang J, Zhi X, Zhang Y, Xiu Q, Ma J, Zhang L and You C: Erlotinib *versus* chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol *12*: 735-742, 2011.

7 Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, Palmero R, Garcia-Gomez R, Pallares C, Sanchez JM, Porta R, Cobo M, Garrido P, Longo F, Moran T, Insa A, De Marinis F, Corre R, Bover I, Illiano A, Dansin E, de Castro J, Milella M, Reguart N, Altavilla G, Jimenez U, Provencio M, Moreno MA, Terrasa J, Muñoz-Langa J, Valdivia J, Isla D, Domine M, Molinier O, Mazieres J, Baize N, Garcia-Campelo R, Robinet G, Rodriguez-Abreu D, Lopez-Vivanco G, Gebbia V, Ferrera-Delgado L, Bombaron P, Bernabe R, Bearz A, Artal A, Cortesi E, Rolfo C, Sanchez-Ronco M, Drozdowskyj A, Queralt C, de Aguirre I, Ramirez JL, Sanchez JJ, Molina MA, Taron M, Paz-Ares L; Spanish Lung Cancer Group in collaboration with Groupe Français de Pneumo-Cancérologie and Associazione Italiana Oncologia Toracica: Erlotinib *versus* standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol *13*: 239-246, 2012.

8 Omuro AM, Kris MG, Miller VA, Franceschi E, Shah N, Milton DT and Abrey LE: High incidence of disease recurrence in the brain and leptomeninges in patients with nonsmall cell lung carcinoma after response to gefitinib. Cancer *103*: 2344-2348, 2005.

9 Heon S, Yeap BY, Britt GJ, Costa DB, Rabin MS, Jackman DM and Johnson BE: Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. Clin Cancer Res *16*: 5873–5882, 2010.

10 Eichler AF, Kahle KT, Wang DL, Joshi VA, Willers H, Engelman JA, Lynch TJ and Sequist LV: EGFR mutation status and survival after diagnosis of brain metastasis in nonsmall cell lung cancer. Neuro Oncol *12*: 1193-1199, 2010.

11 Langer CJ and Mehta MP: Current management of brain metastases, with a focus on systemic options. J Clin Oncol *23*: 6207-6219, 2005.

12 Sundstrom JT, Minn H, Lertola KK and Nordman E: Prognosis of patients treated for intracranial metastases with whole-brain irradiation. Ann Med *30*: 296-299, 1998.

13 Jamal-Hanjani M and Spicer J: Epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of epidermal growth factor receptor–mutant non–small cell lung cancer metastatic to the brain. Clin Cancer Res *18*: 938-944, 2012.

14 Pao W, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, Kris MG and Varmus H: Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med *2*: e73, 2005.

15 Kobayashi S, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG and Halmos B: EGFR mutation and resistance of non–small-cell lung cancer to gefitinib. N Engl J Med *352*: 786-792, 2005.

16 Engelman JA, Zejnullahu K, Mitsudomi T, Song Y, Hyland C, Park JO, Lindeman N, Gale CM, Zhao X, Christensen J, Kosaka T, Holmes AJ, Rogers AM, Cappuzzo F, Mok T, Lee C, Johnson BE, Cantley LC and Jänne PA: MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science *316*: 1039-1043, 2007.

17 Yano S, Wang W, Li Q, Matsumoto K, Sakurama H, Nakamura T, Ogino H, Kakiuchi S, Hanibuchi M, Nishioka Y, Uehara H, Mitsudomi T, Yatabe Y, Nakamura T and Sone S: Hepatocyte growth factor induces gefitinib resistance of lung adenocarcinoma with epidermal growth factor receptor-activating mutations. Cancer Res *68*: 9479-9487, 2008.

18 Wang W, Li Q, Yamada T, Matsumoto K, Matsumoto I, Oda M, Watanabe G, Kayano Y, Nishioka Y, Sone S and Yano S: Crosstalk to stromal fibroblasts induces resistance of lung cancer to epidermal growth factor receptor tyrosine kinase inhibitors. Clin. Cancer Res *15*: 6630-6638, 2009.

19 Sequist LV, Waltman BA, Dias-Santagata, Digumarthy S, Turke AB, Fidias P, Bergethon K, Shaw AT, Gettinger S, Cosper AK, Akhavanfard S, Heist RS, Temel J, Christensen JG, Wain JC, Lynch TJ, Vernovsky K, Mark EJ, Lanuti M, Iafrate AJ, Mino-Kenudson M and Engelman JA: Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med *3*: 75ra26, 2011.

20 Oxnard GR, Arcila ME, Sima CS, Riely GJ, Chmielecki J, Kris MG, Pao W, Ladanyi M and Miller VA: Acquired resistance to EGFR tyrosine kinase inhibitors in EGFRmutant lung cancer: distinct natural history of patients with tumors harboring the T790M mutation. Clin Cancer Res *17*: 1616-1622, 2011.

21 Hata A, Katakami N, Yoshioka H, Takeshita J, Tanaka K, Nanjo S, Fujita S, Kaji R, Imai Y, Monden K, Matsumoto T, Nagata K, Otsuka K, Tachikawa R, Tomii K, Kunimasa K, Iwasaku M, Nishiyama A, Ishida T and Nishimura Y: Rebiopsy of non-small cell lung cancer patients with acquired resistance to epidermal growth factor receptor-tyrosine kinase inhibitor: comparison between T790M mutation-positive and -negative populations. Cancer *119*: 4325-4332, 2013.

22 Chmielecki J, Foo J, Oxnard GR, Hutchinson K, Ohashi K, Somwar R, Wang L, Amato KR, Arcila M, Sos ML, Socci ND, Viale A, de Stanchina E, Ginsberg MS, Thomas RK, Kris MG, Inoue A, Ladanyi M, Miller VA, Michor F and Pao W: Optimization of dosing for EGFR-mutant non–small cell lung cancer with evolutionary cancer modeling. Sci Transl Med *3*: 90ra59, 2011.

23 Jackman D, Pao W, Riely GJ, Engelman JA, Kris MG, Jänne PA, Lynch T, Johnson BE and Miller VA : Clinical definition of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancer. J Clin Oncol *28*: 357-360, 2010.

24 Nagai Y, Miyazawa H, Huqun, Tanaka T, Udagawa K, Kato M, Fukuyama S, Yokote A, Kobayashi K, Kanazawa M and Hagiwara K: Genetic heterogeneity of the epidermal growth factor receptor in non-small cell lung cancer cell lines revealed by a rapid and sensitive detection system, the peptide nucleic acid-locked nucleic acid PCR clamp. Cancer Res *65*: 7276-7282, 2005.

25 Jackman DM, Holmes AJ, Lindeman N, Wen PY, Kesari S, Borras AM, Bailey C, de Jong F, Jänne PA and Johnson BE: Response and resistance in a non-small-cell lung cancer patient with an epidermal growth factor receptor mutation and leptomeningeal metastases treated with high-dose gefitinib. J Clin Oncol *24*: 4517-4520, 2006.

26 Katayama T, Shimizu J, Suda K, Onozato R, Fukui T, Ito S, Hatooka S, Sueda T, Hida T, Yatabe Y and Mitsudomi T: Efficacy of erlotinib for brain and leptomeningeal metastases in patients with lung adenocarcinoma who showed initial good response to gefitinib. J Thorac Oncol *4*: 1415-1419, 2009.

27 Dhruva N and Socinski MA: Carcinomatous meningitis in non-small-cell lung cancer: response to high-dose erlotinib. J Clin Oncol *27*: 31-32, 2009.

28 Clarke JL, Pao W, Wu N, Miller VA and Lassman AB: High dose weekly erlotinib achieves therapeutic concentrations in CSF and is effective in leptomeningeal metastases from epidermal growth factor receptor mutant lung cancer. J Neurooncol *99*: 283-286, 2010.
29 Hata A, Kaji R, Fujita S and Katakami N: High-dose erlotinib for refractory brain metastases in a patient with relapsed nonsmall cell lung cancer. J Thorac Oncol *6*: 653-654, 2011.
30 Grommes C, Oxnard GR, Kris MG, Miller VA, Pao W, Holodny AI, Clarke JL and Lassman AB: "Pulsatile" high-dose weekly erlotinib for CNS metastases from EGFR mutant non-small cell lung cancer. Neuro Oncol *13*: 1364-1369, 2011.
31 Kuiper JL and Smit EF: High-dose, pulsatile erlotinib in two NSCLC patients with leptomeningeal metastases – one with a remarkable thoracic response as well. Lung Cancer *80*: 102-105, 2013.
32 Weickhardt AJ, Scheier B, Burke JM, Gan G, Lu X, Bunn PA Jr, Aisner DL, Gaspar LE, Kavanagh BD, Doebele RC and Camidge DR: Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non–small-cell lung cancer. J Thorac Oncol *7*: 1807-1814, 2012.
33 Shukuya T, Takahashi T, Naito T, Kaira R, Ono A, Nakamura Y, Tsuya A, Kenmotsu H, Murakami H, Harada H, Mitsuya K, Endo M, Nakasu Y, Takahashi K and Yamamoto N: Continuous EGFR-TKI administration following radiotherapy for non-small cell lung cancer patients with isolated CNS failure. Lung Cancer *74*: 457-461, 2011.

Received October 8, 2014
Revised November 3, 2014
Accepted November 5, 2014